In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

TRYSTAN SANCHEZ, by and through his parents, GERMAIN SANCHEZ and JENNIFER SANCHEZ,	*	No. 11-685V
	*	Special Master Christian J. Moran
	*	Filed: August 26, 2020
Petitioners,	*	
v.	*	Entitlement; DTaP; Leigh's syndrome; mitochondrial disorder; decompensation; genetic mutation; SDHA; remand
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Lisa A. Roquemore, Law Offices of Lisa A. Roquemore, Rancho Santa Margarita, CA, for petitioners;
Jennifer L. Reynaud, United States Dep't of Justice, Washington, DC, for respondent.

PUBLISHED DECISION ON REMAND DENYING COMPENSATION[1]

Following an October 9, 2018 decision by the undersigned special master and a February 11, 2019 Opinion and Order by the Court of Federal Claims, the Federal Circuit vacated the February 11, 2019 judgment and remanded for additional consideration. The undersigned, as the Federal Circuit instructed, has

[1] Because this decision contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). This means the decision will be available to anyone with access to the internet. In accordance with Vaccine Rule 18(b), petitioners have 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material before posting the decision.

considered the parties' new evidence and arguments as well as reconsidered the parties' old evidence and arguments. The undersigned finds that the Sanchezes are not entitled to compensation on their claim that the vaccinations their son, Trystan, received at six-months caused or significantly aggravated his Leigh's syndrome.

The denial of compensation rests upon two independent grounds. First, the evidence shows that Trystan did not experience neurologic deterioration until many weeks after his six-months vaccination. This passage of time in which Trystan appeared neurologically normal exculpates the vaccinations. Second, the Secretary has carried his burden of demonstrating that two genetic mutations solely caused Trystan's Leigh's syndrome.

I. Overview of Events in Trystan's Life

Trystan was born in August 2008, but a critical event happened before he was born. When he was conceived, he inherited from his father a mutation in a gene known as an SDHA gene. Coincidentally, he inherited from his mother a different mutation in the SDHA gene. However, these mutations were not detected for many years. In the litigation, the parties dispute the consequences of these mutations.

After Trystan was born, he received relatively little medical care for his first six months. At the age of six-months, on February 5, 2009, Trystan was seen by a pediatrician who found Trystan to be developing normally. In this appointment, Trystan received a series of vaccinations including a dose of the diptheria-tetanus-acellular pertussis (DTaP) vaccination.

On the day and evening following the vaccination, Trystan cried inconsolably. He also had a hot red mark on his thigh, and developed a fever that ebbed and flowed for a few days.

On February 16, 2009, Trystan was suffering from a common cold. In the course of this illness, he was congested, had a fever, and jerked around in his father's arms. Trystan also contorted his arms.

Trystan had more colds for which his parents brought him to a pediatrician at the end of April 2009 and in May 2009. During this time, Trystan began to lose some developmental skills.

Trystan's parents brought him for medical attention in August 2009. During this appointment, a physician's assistant noticed his lack of development and

referred him to additional medical services. This referral eventually led to an appointment with a neurologist, who also documented problems with Trystan.

For many years, the precise nature of Trystan's illness eluded the doctors who treated him. Eventually, he was diagnosed with Leigh's syndrome. "Leigh Syndrome usually refers to a severe neurological disorder that often presents in the first year of life and is characterized by progressive loss of mental and movement abilities and typically results in death within a couple years." Exhibit 140 (report of Dr. Haas) at 5. A genetic test revealed the mutations with which he was born.

Trystan, today, is developmentally delayed. Specifically, he is described as "[g]lobally delayed but metabolically stable" and experiencing a seizure disorder, muscle hypotonia, and failure to thrive over the past 2-3 years. See exhibit 181 at 2, 10, 23 (Dr. Haas). His condition reflects a child with Leigh's syndrome.

The foregoing summary is intended to provide a general overview about Trystan's life. Additional details are discussed in the context of evaluating the parties' arguments as to whether the DTaP vaccination harmed Trystan. See section VII (Althen prong 2) below.

II. Procedural History

This case has had four different phases. The case began at the Office of Special Masters (part A below). After a decision denying entitlement, the Sanchezes filed a motion for review, moving the case to the Court of Federal Claims (part B below). After judgment against them, the Sanchezes appealed to the Federal Circuit (part C below). The Federal Circuit vacated the judgment and remanded the case back to the Office of Special Masters (part D below).

A. Office of Special Masters

Trystan's parents alleged that before Trystan received his six-months vaccinations, he was developing normally. When he received his vaccinations, he changed. By the time of the petition, Trystan had become developmentally delayed. Pet., filed Oct. 17, 2011, at 11.

Shortly after filing the petition, the Sanchezes submitted evidence to support their claim. The evidence can be divided into three types. Some evidence was in the form of medical records from doctors who treated Trystan. E.g., exhibits 1, 8-12. Other evidence was in the form of affidavits from Trystan's family members, including his mother and father. Exhibits 3-7. Finally, the Sanchezes presented a

report from Lawrence Steinman, a pediatric neurologist, who has presented multiple reports and testified on the Sanchezes' behalf throughout this case. Exhibit 2.

As discussed below, the evidence showed that Trystan was taken to his six-month well-baby checkup with Dr. Philip Brown on February 5, 2009. Exhibit 1 at 44. During this visit, Trystan received the allegedly causal vaccinations.

The medical records also show that on the morning of February 17, 2009, Trystan returned to the pediatrician for an urgent care visit during which he was examined and treated by Physician Assistant Jonathan P. Luna. Mr. Luna diagnosed Trystan with a "[c]ommon cold" and "[v]iral syndrome." Exhibit 1 at 48. Trystan's temperature was 98.9 degrees and "fever" was noted. Id. at 49. Ms. Sanchez told Mr. Luna that Trystan had been coughing and congested with fever. Id. The records do not indicate that Ms. Sanchez told Mr. Luna anything about Trystan exhibiting unusual arm movements or other signs of a neurological condition. See id. at 48-49.

However, in their affidavits, Trystan's family members recollected different events. Most critically, Trystan's father asserted that on the evening of February 16, 2009, Trystan displayed unusual movements:

> Trystan was very hot with a fever of 103.2 and kept crying inconsolably. . . . When I held Trystan in my arms and tried to calm him down, I noticed a changed in Trystan. He felt very stiff and uncomfortable. Originally, I thought he was throwing some kind of fit and trying to show how miserable he felt by stiffening his body. . . . I had never seen a child do that before. Trystan began to hold his arm behind his back with a lot of tension and jerk his head back. When I tried to comfort him and gently put his arm back to the normal position, Trystan would go right back to holding it behind his back again. This lasted for only a few minutes. . . . (We later learned that this was likely a seizure, but we had no idea at the time that it was occurring.) We continued to rock Trystan to sleep and this strange behavior slowly subsided.

Exhibit 4 (Germain Sanchez affidavit, signed Oct. 5, 2011) at 3, ¶ 6.

Mr. Sanchez's assertion is critical because Dr. Steinman relied upon it in his first report. Dr. Steinman acknowledged that when he wrote his first report

(September 28, 2011), doctors had not reached a diagnosis about Trystan. "The diagnosis of Trystan Sanchez'[s] disorder has defied the best medical scientists at three university medical schools as well as other treating physicians for now." Exhibit 2 at 2. Nevertheless, the lack of diagnosis did not prevent Dr. Steinman from offering an opinion. "What we do know, however, is that Trystan Sanchez was given multiple vaccines, he suffered from fever and he suffered from seizures." Id.

Dr. Steinman's statement that "we do know . . . he suffered from seizures" suggests a level of certainty that was inconsistent with an earlier portion of Dr. Steinman's report. In reviewing the events in Trystan's history, Dr. Steinman stated: "Eleven days later in the context of a febrile illness, he *may* have had a seizure, manifest by stiffening and 'holding his arm behind his back with a lot of tension and jerked his head back.'" Id. at 1 (emphasis added).

Regardless, the remainder of Dr. Steinman's report is premised upon Trystan having a seizure. Dr. Steinman summarized his report as presenting an opinion that "the vaccines due to their components, triggered seizures and that if not for this vaccine induced seizure disorder, then Trystan Sanchez would not have suffered such devastating neurological consequences." Id. at 10. Over the next four pages, Dr. Steinman presented theories of how the vaccines could cause seizures. Id. at 10-14. Despite having Mr. Sanchez's description of Trystan's unusual arm movements available to him, nowhere in Dr. Steinman's first report does he suggest that the behavior Mr. Sanchez described in his affidavit constituted dystonia.[2]

The Secretary challenged the Sanchezes' entitlement to compensation in his report, filed pursuant to Vaccine Rule 4 on February 28, 2012. The Secretary maintained that the Sanchezes "have not demonstrated the threshold facts upon which the claim is based. Specifically, petitioners have not shown that Trystan suffered from either seizures or developmental delays within an appropriate temporal relationship to the February 5, 2009 vaccines." Resp't's Rep. at 11. The Secretary commented that no medical record created around February 2009 corroborates assertions made in the affidavits from the Sanchez family. Id. at 12. With his report, the Secretary filed a report from Gerald Raymond, a specialist in

[2] Dystonia is "dyskinetic movements due to disordered tonicity of muscle." Dorland's Illustrated Medical Dictionary 576 (32d ed. 2012).

genetics and neurology, who has written many reports and testified for the Secretary during this case. Exhibit A.

Because the parties and their experts disputed whether Trystan displayed unusual arm movements starting in February 2009, the undersigned received oral testimony from the five family members on May 15, 2012, in San Diego, California.[3] After the hearing, a status conference was held on May 29, 2012.

In the status conference, the undersigned discussed how the parties could assist in resolving factual disputes. The process for bringing forward disputed factual issues had at least three steps. The Sanchezes were instructed to propose a series of facts, citing evidence supporting their assertion of facts. The Sanchezes were directed to transmit their proposal to the Secretary and not to file their proposed submission. The Secretary was instructed to respond to each proposed finding of fact, either agreeing or disagreeing. If the Secretary disputed the proposed assertion, the Secretary was to cite evidence supporting his position. The Secretary was also not expected to file his response. Once the Sanchezes received this document, they could comment. This back-and-forth was expected to continue until the parties presented all their points. Then, and only then, the parties were expected to submit a final version incorporating, in one document, all the arguments regarding any factual disputes. After the parties had engaged in this process for about four months, another status conference was held on October 11, 2012. The parties reported that they were close to finishing this process. Order, issued Oct. 12, 2012.

The parties submitted a document titled "Joint Statement of Uncontroverted Facts" on November 8, 2012. As noted by the Court of Federal Claims, see Sanchez v. Sec'y of Health & Human Servs., 142 Fed. Cl. 247, 252-53 (2019), vacated and remanded, 809 F. App'x 843 (Fed. Cir. 2020) (hereinafter "Opinion and Order"), the description of the facts as "uncontroverted" reflects an imprecise word choice to which the undersigned contributed. The undersigned had intended to set forth a process by which the parties would identify the *material* facts that the parties *genuinely* disputed. The undersigned did not expect that the parties would produce a stipulation about *all* facts because, after all, the parties' dispute about the

[3] In considering the issues on remand, the undersigned has re-read the transcript from the 2012 hearing as well as notes, which record demeanor-based observations.

events in Trystan's life necessitated the May 15, 2012 hearing. Instead, the parties would identify the issues requiring resolution.

To some degree, the parties' Joint Statement was not as helpful as anticipated, and the undersigned recognizes that the instructions could have been more detailed. In the absence of more direct guidance, the parties produced statements such as "*According to* Jennifer [Ms. Sanchez], between her birthday and the next time she took him [Trystan] to the doctor nearly two months later in late April, Trystan lost control of his head." Joint Statement ¶ 17 (citing Transcript ("Tr.") at 78) (emphasis added).[4] The parties could easily agree that transcript page 78 supports the proposition that Ms. Sanchez *testified* that Trystan lost control of his head between February and April. However, the words that Ms. Sanchez spoke during the hearing are not directly material. The more critical question---and the one about which the parties disagreed---was whether, in fact, Trystan lost control of his head between February and April. On this specific point, the undersigned declined to credit Ms. Sanchez's testimony because the records from a pediatrician who saw Trystan at the end of April recorded "no neurological symptoms." See Ruling Finding Facts, issued Apr. 10, 2013, ¶¶ 13-14 (citing exhibit 1 at 50-52).

In the Ruling Finding Facts, the undersigned also found that Trystan did not exhibit arm contortions around February 16-17, 2009. Id. ¶¶ 8-11. The undersigned reasoned that if Trystan had moved his arm unusually, then the Sanchezes would have informed the physician's assistant who saw Trystan on February 17, 2009, and the physician's assistant would have memorialized a complaint in the notes.

On the other hand, the Ruling Finding Facts did credit the witnesses' testimony that on the night following the February 5, 2009 vaccination, Trystan cried inconsolably. He also had a lump on his left thigh and a fever. The fever ebbed and flowed over the next few days. Ruling Finding Facts ¶ 7.

The Ruling Finding Facts directed the parties to provide it to their experts. If the experts assumed facts that were not consistent with the Ruling Finding Facts,

[4] The transcript page numbering runs consecutively across the three hearings in this case but does contain some gaps in the numbering: fact hearing (pages 1-231), entitlement hearing (pages 233-1011), and remand hearing (pages 2000-2179).

then the expert was unlikely to be persuasive. Id. at 16 (citing Burns v. Sec'y of Health & Human Servs., 3 F.3d 415, 417 (1993)).

The Sanchezes filed another report from Dr. Steinman on May 22, 2013. Exhibit 17. However, Dr. Steinman's report seemed to resemble very closely his previous report. For example, Dr. Steinman continued to assert that Trystan had seizures. This prompted an order directing Dr. Steinman to explain the basis for his opinion that Trystan had seizures. Order, issued June 14, 2013.

Dr. Steinman's report did not really answer this question. He stated that Trystan suffered seizures. Exhibit 28 at 2. He also stated that Trystan suffered one continuous process. Id. at 3. In a December 6, 2013 status conference, the Secretary questioned how Dr. Steinman linked an apparently isolated seizure with developmental delay. Thus, the Sanchezes were ordered to file a status report.

The Sanchezes asserted that Trystan had "a process of continuous and/or intermittent seizure activities commencing in February 2009." Pet'rs' Status Rep., filed Dec. 18, 2013, at 4. As evidence of these seizures, the Sanchezes pointed to (1) the inconsolable crying on February 5, 2009; (2) the loud pitched cry and kicking feet on February 16, 2009; (3) the inconsolable crying during March 2009, when his parents watched a boxing match; (4) Trystan's loss of skills by June 1, 2009; (5) inconsolable crying during the August 8, 2009 baby shower; (6) the observation by Ms. Marin-Tucker on August 17, 2009, that Trystan's extremities seemed soft yet rigid; and (7) the development of tremors or twitching between October 7, 2009, and November 12, 2009. Id. at 2. The Sanchezes also pointed to the September 17, 2010 EEG that indicated, to the Sanchezes, partial seizures. Id. at 3 (citing exhibit 1 at 181-82).

The Sanchezes additionally relied upon an August 2, 2010 note from Dr. Friedman. There, Dr. Friedman recorded a history in which Trystan had "one particularly bad night" during which "he would stiffen his arms behind his back, he would jerk his arms and neck . . . Would do this minutes at a time. Dad would try to straighten his arms but they would snap back. . . . After that night, this would come and go." Id. at 2-3 (quoting exhibit 1 at 194). The Sanchezes justified reliance on Dr. Friedman's August 2, 2010 record because the Ruling Finding Facts stated that the parties agreed that records created after the November 12, 2009 visit with Dr. Michelson were accurate.

The parties discussed this status report about Trystan's seizures in status conferences held on January 17 and 28, 2014. The Secretary argued that the Sanchezes' reliance on the history recorded in Dr. Friedman's note was "logical

insanity" in that it was not consistent with the Ruling Finding Facts. The Secretary argued that the Sanchezes' approach would allow them to go to a doctor "today" and set forth a history about Trystan's health in 2009.

A January 31, 2014 order attempted to resolve this dispute by distinguishing between histories and findings in the reports from doctors. The undersigned stated that:

> paragraph 24 of the Findings of Fact was intended to state that the medical records created after Trystan's visit with Dr. Michelson were accurate to the extent that the medical records described Trystan's contemporaneous condition. The Sanchez[es'] account of remote events in Trystan's life to Dr. Friedman does not qualify as a contemporaneous record.

Order, issued Jan. 31, 2014. Accordingly, the parties were directed to confirm that their experts were not relying upon Dr. Friedman's record for the basis of events in Trystan's life between February 2009 through November 2009.

The Secretary responded to Dr. Steinman's reports by presenting another report from Dr. Raymond.[5] Dr. Raymond suggested that Trystan might benefit from genetic testing because Trystan might have a mutation in his mitochondria. Exhibit E at 2. Dr. Raymond wondered how Dr. Steinman could say that the vaccinations caused Trystan's problems when the doctors have been unable to say what Trystan's diagnosis is. Id. The Secretary also presented a report from Edward Cetaruk, a medical toxicologist, who made the same point. Exhibit G at 17. Based, in part, on the criticisms from the Secretary's experts, the undersigned began to question whether a reasonable basis supported the claims set forth in the petition. Order, issued May 13, 2014.

The Sanchezes produced another report from Dr. Steinman. Exhibit 36. In response to Dr. Raymond's suggestion that Trystan might have a genetic mutation

[5] Although this decision does not mention each report from every expert, the undersigned has reviewed and considered all reports submitted into evidence. See Moriarty v. Sec'y of Health & Human Servs., 844 F.3d 1322, 1330 (Fed. Cir. 2016) (noting that the Vaccine Act requires a special master to consider all relevant medical and scientific evidence of record).

affecting his mitochondria, Dr. Steinman offered a hypothetical opinion that largely has become the Sanchezes' claim:

> [If Trystan had a genetic mutation,] one should remember that there had been no issues related to this mutation prior to the vaccines. Consequently, just in parallel with analysis of what triggers clinical deficits in mitochondrial disorders, it can be argued that this mutation was significantly aggravated by the vaccines, which then progressed to a clinical picture with the subsequent issues. We know that in many metabolic disorders a stress like vaccination or in the case of organic acidemias a protein load, will trigger neurologic deficits.

Exhibit 36 at 2. Dr. Steinman repeated this point later in his report, stating that as an expert, he felt compelled to reexamine the evidence. Based upon the evidence, Dr. Steinman wrote that "there is a plausible line of reasoning that Trystan Sanchez had a mitochondrial disorder that was not expressed prior to his vaccinations; and, his vaccinations significantly aggravated this disorder." Id. at 11.

In developing this account, Dr. Steinman again presented a chronology of events in Trystan's life. In doing so, Dr. Steinman cited an August 7, 2012 report from Dr. Haas. Dr. Haas recounted that Trystan had "acute onset regression and dystonia at six months of age, following vaccination, which repeated with the next set of vaccines at 12 months." Id. at 13 (quoting exhibit 26 at 3). As will be discussed later, Trystan's dystonia (or lack thereof) is a prominent issue on remand.

Three months before the start of a hearing previously scheduled for September 10-12, 2014, the Sanchezes requested a continuance for the hearing so that Trystan could have the whole exome sequencing performed as Dr. Haas recommended. Pet'rs' Status Rep., filed June 23, 2014. The Sanchezes hoped that the sequencing would provide clarity as to Trystan's illness. Id. Based on the Sanchezes' request, the hearing dates were postponed to May 2015. Order, issued July 8, 2014. The Sanchezes were ordered to file the results of the genetic testing as soon as they became available. Order, issued July 21, 2014.

The Sanchezes submitted the results from the first set of testing as exhibit 53 and a report from Dr. Haas about those results as exhibit 54. The genetic testing showed that Trystan had a heterozygous mutation in the SDHA gene, the c.667delG mutation. Exhibit 53 at 1-2. Dr. Steinman explained:

> As the test results indicate, developmental regression, hypotonia, spasticity, dystonia, seizures, high T2 W signal, basal ganglia abnormalities and periventricular white matter changes could be associated with an SDHA-related disorder. I would add IF he were homozygous, he could have a mitochondrial disease known as Leigh syndrome. However, currently, the test results do not show that Trystan is homozygous.

Exhibit 55 at 1. Dr. Steinman noted that Dr. Haas requested additional genetic testing. Dr. Steinman added, "as indicated in my last supplemental expert report, if the additional blood testing supports mitochondrial issues such as Leigh's syndrome or if Dr. Haas determines that there is a mitochondrial disorder based upon the clinical findings, my last supplemental opinion, dated May 24, 2014, addressed such occurrence." Id.

The Sanchezes filed testing identifying Trystan's genetic mutations on January 23, 2015. Exhibit 59. In the ensuing status conference, the Secretary emphasized that the genetic testing further undermined the reasonable basis for continuing the case. However, the Sanchezes wanted to press forward. The parties noted that they needed additional expert reports, although they also decided to retain the May 2015 hearing date at that time. Order, issued Feb. 4, 2015. On February 20, 2015, the Sanchezes filed a status report requesting that the May 2015 hearing be postponed. The Secretary did not object to this request. Order, issued Mar. 3, 2015. Accordingly, the undersigned cancelled the May 2015 hearing and scheduled a status conference for late April 2015 to discuss the next steps. Id.

During the April 2015 status conference, the undersigned stated a concern that the newly-filed information regarding Trystan's genetic mutations undermined the Sanchezes' claim of a vaccine injury because Trystan's clinical course may be consistent with what is expected based on the mutations alone. Order, issued May 8, 2015, at 1. The parties also discussed how the burden of proof is allocated in genetics cases with the Sanchezes asking whether they as petitioners have the burden to show how Trystan would have been but for the vaccination. The undersigned encouraged the Sanchezes to develop evidence that would show that Trystan was worse than would be otherwise expected for someone with his genetic

mutations. Id.[6] Accordingly, the Sanchezes requested additional time to procure genetic testing from Trystan's siblings since the results might shed light on how Trystan's disease course may be different than what can be expected for someone with his same genetic mutations. Id. The Sanchezes' request was granted, and a status conference was set for June 2015, to discuss the results from the new genetic testing and the Sanchezes' next steps. Id. at 1-2.

The Sanchezes stated that the additional genetic testing would not be complete before the end of July 2015, and that the Sanchezes currently had an appointment scheduled with their treating physician for late August 2015, to discuss the results of this additional genetic testing. Pet'rs' Status Rep, filed June 23, 2015. The undersigned set a status conference for the end of September 2015. Order, issued June 24, 2015.

During the September 2015 status conference, the Sanchezes contended that the Federal Circuit's opinion in Paluck v. Sec'y of Health & Human Servs., 786 F.3d 1373 (Fed. Cir. 2015), helped to support the reasonable basis for their claim because, in that case, the Federal Circuit concluded that a vaccination can aggravate a mitochondrial disorder. In addition, the parties discussed the need for additional expert reports in light of the new information regarding Trystan's genetic mutations. Order, issued Oct. 1, 2015.

Over the course of the next year, both the Sanchezes and the Secretary filed additional reports from their respective experts. The Sanchezes added a new expert with a specialty in mitochondrial disorders, Dmitriy Niyazov, whose first report is exhibit 68. Dr. Niyazov opined that Trystan "experienced developmental regression, caused by a vaccine reaction, which exacerbated his deficient cellular energy metabolism due to his SDHA gene mutations." Exhibit 68 at 7. For the initial manifestation of Trystan's Leigh's disease,[7] Dr. Niyazov identified the

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[6] In April 2015, it appeared that the burden of showing how the vaccinee would have developed "but for" the vaccination fell to petitioners. See Locane v. Sec'y of Health & Human Servs., 685 F.3d 1375, 1379 (Fed. Cir. 2012).

However, after the Federal Circuit remanded this case, the Federal Circuit declared that the petitioners do not bear the burden of proof on this point for cases involving genetic disorders. Sharpe v. Sec'y of Health & Human Servs., 964 F.3d 1072, 1084-85 (Fed. Cir. 2020).

[7] Dr. Haas confirmed Trystan's diagnosis of Leigh's disease. See exhibit 62 at 5.

"inconsolable crying along with the fever" that occurred within 48 hours of the February 5, 2009 vaccination. Id. at 8. He continued:

> This inflammatory response served as the initial catabolic event in Trystan that triggered a gradual process of developmental regression and aggravation leading to [Leigh's syndrome] over the next several months which has become more evident around June 1, 2009 (inconsolable crying, hypotonia, arm contortion, etc.). However developmental regression was slowly developing ever since the crying and fever took place as the result of the vaccination . . . .

Id.

Dr. Niyazov also addressed whether the genetic mutations could inform an assessment of how Trystan would have developed but for the vaccinations. He opined that due to "variable expressivity" and "incomplete penetrance," Trystan may not have developed Leigh's syndrome at all. Id. at 10. Dr. Niyazov heavily relied upon the Levitas article to support his opinion. Id.; see Aviva Levitas et al., *Familial neonatal isolated cardiomyopathy caused by a mutation in the flavoprotein subunit of succinate dehydrogenase*, 18 Eur. J. Hum. Genetics 1160 (2010), filed as exhibit 79.

Dr. Steinman's report roughly presented the same view as taken by Dr. Niyazov in his report. Dr. Steinman's conclusion was "if not for the vaccinations on Feb. 5, 2009, Trystan Sanchez would not be suffering from Leigh's disease." Exhibit 95 at 1. Much of Dr. Steinman's December 10, 2015 report repeats information presented in his previous reports, reflecting Dr. Steinman's intention to present a comprehensive report. For example, Dr. Steinman referenced his September 13, 2013 report (exhibit 28) in which he stated Trystan began to have seizures on February 16, 2009, when he was running a fever, having difficulty breathing, crying with a loud-pitched cry, jerking around, and startling awake. Id. at 28 (citing Ruling Finding Facts ¶ 8). Like his earlier report, Dr. Steinman again stated that Dr. Haas's August 7, 2012 report provided detail about Trystan's condition on February 16, 2009. Dr. Steinman reproduced the report in which Dr. Haas stated, in part, "11 days after the vaccination, [Trystan] had an episode of 'contortion' in the upper limbs." Id. at 39 (reproducing exhibit 26 at 1). Similarly, Dr. Steinman cited a report from Dr. Haas that describes Trystan as having "acute regression associated with significant dystonia at 6 months of age following vaccination. He subsequently had a second episode of developmental regression

12 months later." Id. at 16 (citing exhibit 54 at 1-2).[8] Although Dr. Steinman recognized that Dr. Haas described Trystan as having dystonia following his six-month vaccinations; that Dr. Friedman noted Trystan had dystonia on August 2, 2010 (exhibit 95 at 11, relying upon exhibit 1 at 198); and that Trystan's genetic mutations are associated with dystonia (exhibit 95 at 14, relying upon exhibit 53 at 1-4), Dr. Steinman did not suggest that Trystan suffered dystonia on February 16, 2009.

In response to these two reports and to address the genetic testing, the Secretary obtained a report from Dr. Raymond. Dr. Raymond concluded that Trystan is "a child with Leigh syndrome secondary to mutations in the gene SDHA. This is the sole cause of his neurologic condition and the onset was not caused by immunizations received and his disease course is consistent with the condition and was not aggravated by the receipt of vaccination." Exhibit H at 8. The primary basis for Dr. Raymond's opinion was that Trystan's case matched a case reported by Parfait in that both Trystan and the Parfait subject had a compound heterozygous mutation. Id. at 3.

The parties then obtained additional reports from the experts. Essentially, these reports reinforced the themes from the previous reports. Dr. Niyazov asserted that mutations can present differently, benignly or pathogenically, and relied upon Levitas. See exhibit 102. In contrast, Dr. Raymond relied upon Parfait as a report involving a child very similar to Trystan and the reports that companies that produce genetic reports characterize Trystan's mutations as pathogenic. See exhibit P.

After the parties finished the submission of expert reports, they filed briefs. The Sanchezes filed their brief on July 7, 2017. The Secretary responded on September 1, 2017.

In the pre-hearing status conference, the undersigned defined the amount of time the parties had to elicit testimony from their own witnesses on direct examination, or from the other party's witness on cross-examination. See order, issued Nov. 27, 2017, at 3.

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[8] While Dr. Steinman accurately cites Dr. Haas's November 11, 2014 report as saying that Trystan had dystonia at 6 months of age (exhibit 54 at 1-2), Dr. Haas has carried this history forward from his first report. See exhibit 26 at 3.

A four-day hearing was held on December 4-7, 2017. During the hearing, the Sanchezes solicited testimony from their two expert witnesses: Dr. Steinman and Dr. Niyazov. The Secretary solicited testimony from four expert witnesses: Dr. Raymond, Dr. Stephen McGeady, Dr. Cetaruk, and Professor Dean Jones. The hearing ended half a day early, with both parties and the undersigned not using all their allotted time. Among other issues, the evidence concerning Trystan's arm contortions and possible dystonia were discussed at the hearing. Specifically, Dr. Steinman characterized Trystan's "arm contortions" occurring after the vaccination when he was six-months old as dystonia. Tr. 357 ("dystonic posturing of his arm"). He further discussed what he believes was Trystan's dystonia as being part of the typical progression of Leigh's syndrome. Tr. 354. On this basis, Dr. Steinman concluded that the presence of dystonia during this time "added weight" to evidence showing that the vaccination was a causal "environmental trigger" of Trystan's development of Leigh's syndrome. Tr. 358. Furthermore, he viewed what he characterized as the dystonic posturing of Trystan's arm as an indicator of a seizure occurring at this time. Tr. 357.

The undersigned found that the Sanchezes were not entitled to compensation in a decision issued on October 9, 2018. The decision began with a statement of facts from Trystan's life. In doing so, the decision attempted to summarize the April 10, 2013 Ruling Finding Facts. For example, the decision explained that the undersigned had found notations in medical records created contemporaneously more persuasive than testimony provided later.

However, in a critical aspect, the October 9, 2018 decision deviated from the April 10, 2013 Ruling Finding Facts. The Ruling Finding Facts stated that around February 17, 2009, "Trystan did not begin to exhibit arm contortions." Ruling Finding Facts ¶ 11. However, the October 9, 2018 decision stated that around February 15, 2009, Trystan's "arms contorted and he was jerking around. However, these movements were of the type typically displayed by an infant suffering from a cold." Sanchez v. Sec'y of Health & Human Servs., No. 11-685V, 2018 WL 5856556, at *4 (Fed. Cl. Spec. Mstr. 2018), mot. for rev. denied, 142 Fed. Cl. 247, 252-53 (2019), vacated and remanded, 809 F. App'x 843 (Fed. Cir. 2020) (hereinafter "Decision"). The October 9, 2018 decision did not explain this inconsistency.

The October 9, 2018 decision also modified the April 10, 2013 Ruling Finding Facts in one other way, although this change is less important. The April 10, 2013 Ruling stated that Trystan began to lose milestones between May 17, 2009, to June 17, 2009, and specified the mid-point of this range (June 1, 2009).

Ruling Finding Facts ¶¶ 18, 20. However, in the December 2017 hearing, the Sanchezes brought forward evidence suggesting that parents might not immediately detect the loss of a child's milestones. Tr. 438-39. Therefore, the October 9, 2018 adjusted the loss of milestones to "the beginning of May 2009, at the earliest." Decision at 8, 2018 WL 5856556, at *4.

After completing a statement of facts about Trystan's life, the decision set out the procedural history, the standards for adjudication, and an overview about genetics (Sections II-IV). The Analysis section (section V) was divided into three parts. In part A, the undersigned found that the Sanchezes showed that a vaccination could aggravate an underlying mitochondrial disorder. In part B, the undersigned found that the Sanchezes did not establish that the vaccinations affected Trystan's mitochondrial disorder for two reasons. First, the manifestation of neurologic delay, which was no earlier than May 1, 2009, occurred too long after the February 5, 2009 vaccination. Second, during the interim, Trystan experienced infections that could have caused his metabolic decompensation. In part C, the undersigned reviewed the genetic evidence, the arguments from Dr. Niyazov about Levitas, and the arguments from Dr. Raymond about Parfait. The conclusion was that "the Secretary provided persuasive evidence to show that Trystan's mutations were expected to cause serious mitochondrial disease . . . [and] that Trystan's actual course is entirely consistent with what is known about his genetic mutations." Decision at 40-41, 2018 WL 5856556, at *25.

B. Court of Federal Claims

The Sanchezes disagreed with the decision by filing a motion for review on November 8, 2018. In their motion for review, the Sanchezes argued that the undersigned committed reversible error for three reasons. First, the Sanchezes argued that the undersigned failed to draw reasonable inferences regarding the timing of Trystan's symptoms, and erroneously did not credit the Sanchezes' oral testimony or reports to various medical providers regarding changes in Trystan's condition following vaccination. The Sanchezes also highlighted the undersigned's acknowledgement of Trystan's arm contortions in February 2009 following the vaccination and argued that the conclusion that these were consistent with a cold (and not necessarily neurological decline) was also in error. Second, the Sanchezes argued that the undersigned disregarded the Federal Circuit's findings in Paluck v. Sec'y of Health & Human Servs., 786 F.3d 1373 (Fed. Cir. 2015), or alternatively disregarded evidence regarding the acceptable timing for the onset of neurodegeneration. Finally, the Sanchezes argued that the undersigned erroneously disregarded evidence of challenge-rechallenge.

In a response filed on December 7, 2018, the Secretary first argued that the undersigned's findings regarding the onset of loss of skills were supported by reasonable inferences because: (1) deeming the earlier, rather than later, medical records as comparatively more persuasive was not arbitrary or capricious; (2) the undersigned's determination that Trystan's February 2009 symptoms were consistent with a cold was supported by the record; and (3) the 2009 calendar entries used by petitioners to support their claim are unreliable. Second, the Secretary argued that the undersigned properly found that Trystan's neurodegeneration did not occur within a medically acceptable time frame sufficient to infer causation. The Secretary argues this primarily because Trystan's first clear sign of neurodegeneration (loss of skills) occurred months after vaccination, and the assertion that other earlier behavior, such as inconsolable crying, indicate neurodegeneration that ebbed and flowed following the vaccination was merely speculative. Finally, the Secretary argued that petitioners' reliance on Paluck is misplaced because, unlike in that case, the undersigned did not set a "hard and fast" time constraint for the onset of neurodegeneration and instead properly weighed evidence regarding the timing of Trystan's indicator of neurodegeneration (skill loss) and whether this supported an inference of causation.

Judge Campbell-Smith issued an opinion denying the motion for review on February 11, 2019. In so doing, the Court found that the undersigned did not err in giving little weight to or emphasis on the day planner evidence, given that petitioners did not provide arguments as to the relevance of this evidence, and that the differences in recitations of facts that petitioners argued against were the result of the undersigned giving greater weight to contemporaneous medical records than petitioners' testimony.

With respect to the causation analysis, the Court identified five key issues raised by petitioners: (1) challenge-rechallenge; (2) findings regarding onset of neurodegeneration; (3) effect of the Paluck II decision; (4) evidence of colds and infections and petitioners' failure to address the alternate cause issue; and (5) the undersigned's consideration of evidence of arm contortions. First, the Court found that though the challenge-rechallenge issue was not mentioned in the undersigned's decision, he need not address all of petitioners' arguments and he had already found that the relevant symptoms had not occurred, making the challenge-rechallenge argument moot. Second, the finding regarding onset of neurodegeneration was not arbitrary or capricious. Third, the evidentiary record in this case was substantially different than that of Paluck II; thus, Paluck II did not dictate a finding of entitlement in this case. Additionally, the undersigned did not

use the temporal measure rejected in Paluck II and did not err in his evaluation of the expert testimony under Paluck II. Fourth, the undersigned did not err in finding that petitioners' arguments regarding colds and infections as an alternate cause were inadequate. Fifth and finally, though the undersigned changed his finding between the Ruling Finding Facts and entitlement decision regarding the occurrence of arm contortions, he maintained that these arm contortions did not indicate of a neurological condition or cause. Thus, the motion for review was denied and judgment entered.

C. Federal Circuit

The Sanchezes filed their notice of appeal to the Federal Circuit on April 9, 2019. In their appellate brief, filed on May 24, 2019, the Sanchezes argued: (1) that the undersigned failed to consider the totality of the record, including Dr. Niyazov's expert testimony, regarding the onset of neurodegeneration adequately, and that Judge Campbell-Smith failed to examine all the evidence in determining whether the undersigned committed legal error on this point; (2) that the undersigned erroneously failed to address evidence of challenge-rechallenge; and (3) that Paluck dictated a finding of entitlement in this case.

In response, the Secretary argued first, that petitioners' arguments amounted to asking the Federal Circuit to reweigh evidence and that the undersigned correctly found (1) that petitioners did not establish by preponderant evidence that three months was a medically acceptable time frame for onset, and (2) the undersigned's conclusion that Trystan's first manifestation of Leigh's syndrome was his loss of skills three months post-vaccination was reasonable. Second, the Secretary argued that there was no evidence of challenge-rechallenge in this case. Finally, the Secretary argued that the evidentiary record in this case is substantially different from Paluck, making petitioners' reliance on that case misplaced.

After holding oral arguments, the Federal Circuit issued its opinion on April 7, 2020, remanding the case for reconsideration on multiple issues. As a preliminary issue, the Federal Circuit ruled that the differences between the evidentiary records of this case and Paluck are substantial enough "such that the outcome of this case is not dictated by Paluck." Sanchez v. Sec'y of Health & Human Servs., 809 F. App'x 843, 852 (Fed. Cir. 2020). Thus, on that question, the Federal Circuit rejected the Sanchezes' arguments.

However, for other issues, the Federal Circuit was more receptive to the Sanchezes' contentions. The Federal Circuit first identified a "significant" discrepancy between the undersigned's Ruling Finding Facts and recitation of facts

in Decision regarding the presence of arm contortions in February 2009. Id. at 852-53. Specifically, the Court stated:

> Importantly, because of the change in the findings made with respect to the arm contortions, the special master's finding that Trystan's behavior on the night of February 16 was consistent with a cold is not supported by expert testimony that specifically addressed the arm contortions. Because this issue is of central importance to the causation analysis, it is necessary to remand for further consideration of the causation issue in light of the special master's findings in 2018 regarding Trystan's arm contortions.

Id. at 853.

Second, the Federal Circuit directed the undersigned to revisit his analysis of Althen prongs 2 and 3, specifically "whether there was a logical sequence of cause and effect linking Trystan's vaccinations and his injuries as well as a proximate temporal relationship between the vaccinations and the onset of injuries" and "whether Trystan's infections between February and May of 2009 caused the manifestation of his Leigh's syndrome, independent of his vaccinations." Id. The Federal Circuit noted that the undersigned "treated [Althen prongs 2 and 3] together as being directed to the single issue of causation," but specified that the undersigned should make explicit findings with respect to each of these considerations separately on remand. Id. In the event that the undersigned finds that the Sanchezes have made out a prima facie case, he should then address whether Trystan's post-vaccination infections triggered the manifestation of his Leigh's syndrome, independent of the vaccinations. Id. at 853-54.

Third, the Federal Circuit found that the undersigned had not "implicitly rejected" the challenge-rechallenge argument in his decision and that "the special master should address that theory expressly on remand." Id. at 854. The Federal Circuit specified that the factual findings upon which the entitlement decision was based pre-dated expert testimony, much of which asserted challenge-rechallenge. Additionally, the Federal Circuit noted that the two medical reports from Ms. Marin-Tucker, upon which the undersigned relied in coming to his factual conclusion that Trystan did not suffer additional loss of skills following his August 2009 vaccinations, may suggest slight differences or increases with respect to loss of skills. Id.; see Ruling Finding Facts at 15 n.11 (finding against additional neurological symptoms following Trystan's August 2009 vaccinations based on

Ms. Marin-Tucker's reports of the Sanchezes denying "any new complaints" but reporting "no improvement either" at Trystan's October 2009 appointment) (citing exhibit 1 at 57). The Federal Circuit directed the undersigned to explicitly address challenge-rechallenge in light of these medical reports. Id.

Finally, the Federal Circuit invited further consideration of medical evidence or literature relevant to whether, because of Trystan's genetic mutations, "the timing and severity of his Leigh's syndrome would have been the same, regardless of the effect of the vaccinations." Id. The Federal Circuit noted that this issue was left open at the end of the entitlement decision and that, given how much time has passed since the decision was issued and the ever-evolving nature of genetics research, the undersigned may wish to consider additional evidence related to this aspect of the case. Id.

D. Office of Special Masters on Remand

When the case returned to the Office of Special Masters, the parties through their attorneys and expert witnesses worked quickly. After the mandate from the Federal Circuit issued, the undersigned proposed a schedule that allowed for the submission of supplemental reports in advance of a hearing. Orders, issued June 3, 2020 and June 12, 2020. As part of this proposed schedule, the undersigned also ordered the Sanchezes to file a status report answering certain questions regarding updates on Trystan's status, including updated medical records and Trystan's Individualized Education Plan, and indicating whether they anticipated filing supplemental expert reports. Order, issued June 3, 2020. The undersigned ordered the Secretary to submit a status report indicating whether he anticipated filing a supplemental expert report. Id. The Sanchezes and the Secretary filed their status reports on June 8, 2020, and June 10, 2020, respectively. They both indicated an intention to file supplemental expert reports and agreed to the undersigned's proposed pre-hearing schedule. The Sanchezes also filed additional updated medical records and Trystan's Individualized Education Plan.

The Sanchezes submitted initial expert reports from Dr. Steinman (exhibit 185) and Dr. Niyazov (exhibit 189), and the Secretary submitted an initial expert report from Dr. Raymond (exhibit P). They also submitted responsive reports. Exhibits 195, 196, and Q.

A prehearing status conference was held on July 7, 2020, to discuss proceedings for the hearing. In this status conference, the undersigned asked the attorneys whether the undersigned might ask questions of the expert witnesses first, followed by each party's questioning. Both attorneys agreed to this process.

In hearings, special masters are permitted to be inquisitorial. See Doe v. Sec'y of Health & Human Servs., 76 Fed. Cl. 328, 334 (2007) (commenting on the "active role of the Special Master in questioning witnesses"); Hines v. Sec'y of Health & Human Servs., 21 Cl. Ct. 634, 648 (1990), aff'd, 940 F.2d 1518 (Fed. Cir. 1991) ("The Special Master is not required to be a 'potted plant' at the hearing . . . Rather, the legislative history of the newly-amended Vaccine Act emphasizes that '[t]he system is intended to allow the proceedings to be conducted in an "inquisitorial" format'. . . ." (quoting 135 Cong. Rec. H9476 (daily ed. Nov. 21, 1989))).

A hearing was held on July 9, 2020, during which the experts testified remotely via videoconferencing. Though the undersigned set aside two days for the hearing, the parties confirmed that they had no further questions for witnesses at the conclusion of the first day, and the hearing ultimately only lasted for one day.

After the hearing, on July 10, 2020, the undersigned issued an order for post-hearing briefs, which outlined various procedural and substantive questions for the parties to address. These questions were tailored to address the remand issues presented by the Federal Circuit and specific items of relevance that arose as part of the experts' testimony at the hearing. On an expedited schedule, the parties submitted two rounds of briefs simultaneously. The parties submitted their first briefs on July 29, 2020, and they submitted their reply briefs on August 5, 2020. Along with their initial post-hearing brief, the Sanchezes submitted additional medical literature aimed at addressing certain points in the undersigned's briefing order. The Secretary did not object to this additional medical literature submitted after the official closing of the evidentiary record. Resp't's Status Rep., filed July 31, 2020. With the parties' briefs and reply briefs submitted, the case is again ready for adjudication.

III. Qualifications of Experts

The adjudication begins with a review of the qualifications of the six people whom the parties have advanced as experts. Because the Sanchezes advance the backgrounds of their experts to support their claim (see, e.g., Pet'rs' Remand Br. at 12) and because special masters may consider the background of a person offering opinion testimony, the qualifications are set forth below. As part of the review, the undersigned also has attempted to search for commentary about each person's past testimony even-handedly. See Greene v. Sec'y of Health & Human Servs., 146 Fed. Cl. 655 (2020) (noting that a failure to consider the (lack of) expertise for the

Secretary's experts in the context of considering the (lack of) expertise for the petitioner's experts was arbitrary and capricious).

A. The Sanchezes' Experts

Initially, the Sanchezes relied upon Dr. Steinman. After Trystan's Leigh's syndrome was diagnosed, they added a second expert, Dr. Niyazov.

1. Lawrence Steinman

Dr. Steinman has often been retained by petitioners and special masters have become accustomed to reviewing his opinions. Dr. Steinman graduated from the medical school at Harvard University. He was a resident in pediatrics at Stanford University Hospital in 1974. He had fellowships from 1975-77, including one at the National Institutes of Health. In 1977-80, he was a resident in pediatric and adult neurology at the Stanford University Hospital. Beginning in 1980, Dr. Steinman served in various academic roles, primarily at Stanford University. From 2002 to 2011, he chaired the Stanford University program in immunology. From 2008 to the present, he was the incumbent of the George A. Zimmerman Chair as professor of neurological sciences, neurology, and pediatrics. Exhibit 168 (Dr. Steinman's curriculum vitae). He became board-certified in neurology in 1984.

Dr. Steinman's research has focused on multiple sclerosis. The National Multiple Sclerosis Society and the American Academy of Neurology awarded him the John M. Dystel prize for outstanding contributions in multiple sclerosis research in 2004. Seven years later, the International Federation of Multiple Sclerosis Societies awarded him the Charcot Prize for lifetime achievement in multiple sclerosis research. Many of the more than 500 articles Dr. Steinman has written or co-written concern how the immune system may cause demyelinating diseases such as multiple sclerosis. See exhibit 168, passim.

While much of Dr. Steinman's career has focused on multiple sclerosis, his earlier work involved subjects much closer to the issues involved in the pending case. Dr. Steinman researched the pertussis vaccine and obtained one or two patents related to the pertussis vaccine. Tr. 244-25. Dr. Steinman also discovered a mitochondrial disease. Tr. 247.

Other special masters have noted that, as Dr. Steinman's research and administrative responsibilities have increased, Dr. Steinman's participation in patient care has decreased. E.g., Rolshoven v. Sec'y of Health & Human Servs., No. 14-439V, 2018 WL 1124737, at *6 (Fed. Cl. Spec. Mstr. Jan. 11, 2018)

(indicating that Dr. Steinman sees 10-20 patients per month); Blackburn v. Sec'y of Health & Human Servs., No. 10-410V, 2015 WL 425935, at *7 (Fed. Cl. Spec. Mstr. Jan. 9, 2015) (stating that, due to a focus on research, Dr. Steinman has seen "considerably fewer patients in the last five years than he saw earlier in his career" and "[d]uring the last five years, has only seen patients approximately one month out of the year"); see also Tr. 2055 (Dr. Steinman: "my different responsibilities have varied with the decade and my other activities").

In their briefing, the Sanchezes advance Dr. Steinman as an expert in pediatrics. See Pet'rs' Remand Br. at 12. While Dr. Steinman is the incumbent of the George A. Zimmerman chair as a professor of neurological sciences, neurology, and pediatrics, the depth of Dr. Steinman's experience in pediatrics, especially with infants, is not especially clear. For example, in the December 2017 hearing, the Sanchezes brought out direct testimony from Dr. Steinman about his qualifications in neurology and immunology. The Sanchezes offered "Dr. Steinman as an expert in neurology and immunology," and he was recognized as an expert in those two fields. Tr. 250. The Sanchezes did not develop any information about Dr. Steinman's background in pediatrics and the Sanchezes did not offer Dr. Steinman as an expert in pediatrics. In the remand hearing, Dr. Steinman stated that he has cared for approximately 100 infants in the last year and sees about six mitochondrial cases per year. Tr. 2014-15. On redirect examination, the Sanchezes elicited vague testimony about Dr. Steinman's work in pediatrics. See Tr. 2056.

With respect to Dr. Steinman's opinions in the field of pediatrics, especially for infants, the undersigned has less confidence in them. One reason is that Dr. Steinman seems to have relatively less direct experience in caring for infants. For example, Dr. Steinman never became board-certified in pediatrics. Tr. 2014. When Dr. Steinman was asked about developmental milestones at various months, he did not answer with much specificity and his demeanor suggested that he could not answer this question spontaneously. Tr. 2016, 2052-54. Nevertheless, the undersigned is not rejecting any of Dr. Steinman's opinions wholesale. The undersigned merely notes that Dr. Steinman appears to have relatively less experience with infants than in other areas, such as multiple sclerosis.

Another reason for some skepticism about Dr. Steinman's opinions is a concern about the way Dr. Steinman has acted as an expert witness. Special masters have indicated that Dr. Steinman presents opinions as an advocate for the petitioners who retain him. See, e.g., D.G. v. Sec'y of Health & Human Servs., No. 11-577V, 2019 WL 2511769, at *182 (Fed. Cl. Spec. Mstr. May 24, 2019);

Chinea v. Sec'y of Health & Human Servs., No. 15-095V, 2019 WL 1873322, at *19 (Fed. Cl. Spec. Mstr. Mar. 15, 2019), mot. for rev. denied, 144 Fed. Cl. 378 (2019); Mueller v. Sec'y of Health & Human Servs., No. 06-775V, 2011 WL 1467938, at *19 n.19 (Fed. Cl. Spec. Mstr. Mar. 16, 2011). This observation, too, does not force an automatic rejection of everything that Dr. Steinman says. However, the frequency with which special masters have commented on Dr. Steinman's performance as an expert witness prompts the undersigned to take Dr. Steinman's opinion with, perhaps, an extra grain of salt.

2. Dmitriy Niyazov

While special masters are quite familiar with Dr. Steinman, Dr. Niyazov is new to the Vaccine Program. Tr. 374, 389-90 (describing previous experience in one case or two cases with vaccines). Dr. Niyazov graduated with a distinction in research from the school of medicine for the University of Rochester in 2001. In the next two years, he had an internship and residency in surgery at Emory University School of Medicine. But, he found he did not like that specialty and changed to medical genetics, in which he was a resident from 2005 to 2007. Exhibit 167 (Dr. Niyazov's curriculum vitae); Tr. 374-75.

Beginning in January 2008, he has worked in New Orleans, Louisiana, for the Ochsner Health System as the section head for medical genetics in the department of pediatrics. Exhibit 167. He has also been an instructor for the Tulane University School of Medicine. Id.

Dr. Niyazov focuses on treating mitochondrial disorders. He participates in various organizations and panels about mitochondrial disorders. Tr. 376, 384-85. In December 2017, Dr. Niyazov was treating approximately 16 cases with confirmed Leigh's syndrome and another 25 patients with suspected Leigh's syndrome. Id. 387. Some of these patients live in other countries and have seen on-line presentations. Dr. Niyazov believes that exercise, nutrition, and vitamins can help treat mitochondrial diseases, although the Food and Drug Administration has not approved any of these treatments. Id. 388. Some of Dr. Niyazov's approximately three dozen publications concern mitochondrial disease. See exhibit 167 at 2-6.

In the December 2017 hearing, the Sanchezes offered Dr. Niyazov as an expert in the field of genetics, including mitochondrial disorders, and he was accepted without objection. The Sanchezes did not offer Dr. Niyazov as an expert in the field of pediatrics. Tr. 391.

In the hearing on remand, Dr. Niyazov acknowledged that he is not board-certified in pediatrics. Id. 2064. However, in the last five years, Dr. Niyazov has seen at least 1,000 infants, although not all those children suffered from mitochondrial disease. While Dr. Niyazov works with developmental pediatricians, he was generally familiar with developmental milestones during the first year. Id.

Dr. Niyazov's demeanor suggested that he expressed his opinions sincerely in the sense that Dr. Niyazov honestly believed what he was saying. His opinions regarding genetics, with some exceptions noted below, were grounded in peer-reviewed articles.

When Dr. Niyazov strayed from the fields of genetics and mitochondrial disorders, his opinions were shakier. For example, although Dr. Niyazov opined about oxidative stress, Dr. Niyazov has relatively little experience in that field. See id. 548-49.[9]

Dr. Niyazov has limited experience testifying in the context of the Vaccine Program. However, in the few cases he has been a part of, other special masters have indicated that while his testimony has been credible overall, it has suffered from some inconsistencies. Specifically, one special master stated that he has "waffled" somewhat in his testimony and that his "testimony about the reliability of his records . . . was somewhat inconsistent." Reddy v. Sec'y of Health & Human Servs., No. 13-208V, 2015 WL 5578610, at *17, *20 (Fed. Cl. Spec. Mstr. Aug. 26, 2015). Additionally, another special master mentioned some concern with Dr. Niyazov over either not properly supporting contentions with relevant research literature or overstating the significance of certain studies in coming to his conclusions. See Reed v. Sec'y of Health & Human Servs., No. 08-650V, 2018 WL 6844458, at *66, *87 (Fed. Cl. Spec. Mstr. Dec. 4, 2018).

B. Secretary's Experts

In the December 2017 hearing, the Secretary presented opinion testimony from four people. On remand, the Secretary relies primarily on Dr. Raymond. To

[9] Dr. Niyazov's relative weakness in the field of oxidative stress (especially when compared to the experience of Dean Jones) did not affect the outcome of the Sanchezes' case. The undersigned determined that the Sanchezes could meet their burden regarding Althen prong 1 without establishing the persuasiveness of the oxidative stress theory. Decision at 19-21, 2018 WL 5856556, at *11-12.

a lesser extent, the Secretary also relies upon Dr. McGeady. Thus, their qualifications are reviewed more thoroughly. For the remaining two experts, Dr. Cetaruk and Dean Jones, the review can be more summary because their opinions do not meaningfully affect the issues on remand.

1. Gerald Raymond

Dr. Raymond graduated from the University of Connecticut School of Medicine in 1984. He was first an intern and then a resident in pediatrics at Johns Hopkins Hospital from 1984 to 1986. He then had another residency in neurology and fellowship in developmental neuropathology. His final fellowship, which was from 1990 to 1993, was in genetics and tetralogy at Massachusetts General Hospital. Exhibit M (Dr. Raymond's curriculum vitae).

From 1993 to 2012, Dr. Raymond worked as a pediatric neurologist for the Kennedy Krieger Institute in Baltimore, Maryland. Through this time, he held academic posts in neurology at the Johns Hopkins University School of Medicine, culminating in a tenured position as a professor of neurology. Next, Dr. Raymond became a professor in neurology with tenure at the University of Minnesota School of Medicine for approximately five years. Then, starting in 2017, he became a professor in pediatrics and neurology at the Penn State College of Medicine. Exhibit M at 2; Tr. 779-80.

Dr. Raymond holds board certifications in clinical genetics and in neurology with a special competence in pediatric neurology. According to Dr. Raymond, approximately 12-20 people hold dual certifications in genetics and neurology. From this group, Dr. Raymond mentored 6-10 people. Tr. 785.

In December 2017, Dr. Raymond was spending approximately 60 percent of his time in clinical duties with the remainder of his time being research and administration. Tr. 783. Dr. Raymond estimated that he sees approximately 18-20 patients per week. Tr. 781. His patients include children and adults. Tr. 782. In his previous positions, Dr. Raymond saw six or seven cases of genetically confirmed Leigh's syndrome. He also saw other cases in which the disease was suspected but not confirmed. Tr. 788. At the December 2017 hearing, Dr. Raymond was no longer following these patients with Leigh's syndrome. Tr. 787, 844.

Dr. Raymond focuses his research on adrenoleukodystrophies, which are disorders of the brain's white matter. Tr. 782, 842. Dr. Raymond has not

published any papers on Leigh's syndrome or on mutations in the SDHA gene. Tr. 842.

Dr. Raymond held a board certification in pediatrics from 1991-2005. Exhibit M at 16. He let that certification lapse. Tr. 845, 2114.

Dr. Raymond was offered as an expert in the field of neurogenetics and pediatric neurology. He was accepted without objection. Tr. 789.

Like Dr. Niyazov, Dr. Raymond appeared to offer sincerely held opinions. In the field of genetics, Dr. Raymond's opinions consistently aligned with publications that appeared in peer-reviewed journals. Dr. Raymond avoided offering opinions in fields in which he is not qualified.

The consistency between Dr. Raymond's opinions and the statements found in peer-reviewed literature left the impression that Dr. Raymond was expressing opinions about Trystan's case as he believed them. Although on cross-examination, Dr. Raymond acknowledged that he usually reviews three cases per year for the respondent in Vaccine Program cases, Tr. 845, Dr. Raymond did not appear to be providing testimony simply to advance the Secretary's position.

In previous cases, special masters have considered Dr. Raymond thorough in his review of a petitioner's medical records and in providing ample support through medical literature in composing his reports. Specifically, Dr. Raymond discusses a petitioner's pre-vaccination medical history in detail during his testimony, incorporating it into his opinion. L.M. v. Sec'y of Health & Human Servs., No. 14-714V, 2019 WL 4072130, at *14 (Fed. Cl. Spec. Mstr. July 23, 2019). Dr. Raymond closely evaluates cited medical literature. See Oliver v. Sec'y of Health & Human Servs., No. 10-394V, 2017 WL 747846, at *27 (Fed. Cl. Spec. Mstr. Feb. 1, 2017), mot. for rev. denied, 133 Fed. Cl. 341 (2017), aff'd, 900 F.3d 1357 (Fed. Cir. 2018), reh'g and reh'g en banc denied, 911 F.3d 1381 (Fed. Cir. 2019). In past cases with the undersigned, he has also cogently explained relevant medical concepts, making his testimony and opinions credible. See, e.g., Santini v. Sec'y of Health & Human Servs., No. 06-725V, 2014 WL 7891507, at *1 (Fed. Cl. Spec. Mstr. Dec. 15, 2014), mot. for rev. denied, 122 Fed. Cl. 102 (2015).

2. Stephen J. McGeady

Dr. McGeady received his medical degree from Creighton University in 1967. He was a resident in pediatrics from 1970 to 1972. His fellowship was in

psychiatry / allergy from 1972 to 1974. Beginning in 1974, he served in various academic positions at institutions in Philadelphia, Pennsylvania. From 1996 to 2007, Dr. McGeady was the chief of the allergy, asthma and immunology division for duPont Hospital for Children in Wilmington, Delaware. Exhibit N (Dr. McGeady's curriculum vitae). He became board-certified in pediatrics in 1973. He added a second board, allergy and immunology, in 1975. Tr. 728.

By the December 2017 hearing, Dr. McGeady had attained emeritus status, meaning he was working 1 ½ days per week. Tr. 737. In Dr. McGeady's career, he had seen some children with Leigh's syndrome but maybe not any after 1995. Tr. 738-39.

Other special masters have regarded Dr. McGeady as well-prepared, logical, and understandable in his testimony. Specifically, he has incorporated an extensive knowledge of the record during his testimony. Doe/17 v. Sec'y of Health & Human Servs., No. [redacted]V, 2008 WL 2541188, at *7 (Fed. Cl. Spec. Mstr. May 30, 2008), mot. for rev. denied, 84 Fed. Cl. 691 (2008). Furthermore, he is thought to present his testimony in a way that is logical and can answer questions thoroughly and defend his positions. See Hirmiz v. Sec'y of Health & Human Servs., No. 06-371V, 2014 WL 4638375, at *10 (Fed Cl. Spec. Mstr. Aug. 26, 2014) ("Dr. McGeady was better able to answer questions and defend his opinion."), mot. for rev. denied, 119 Fed. Cl. 209 (2014), aff'd, 618 F. App'x 1033 (Fed. Cir. 2015). Finally, the undersigned has regarded Dr. McGeady in the past as "explain[ing] the basis of his opinions in an understandable way." Jaafar v. Sec'y of Health & Human Servs., No. 15-267V, 2018 WL 4519066, at *3 (Fed. Cl. Spec. Mstr. Aug. 10, 2018).

3. Edward Cetaruk

Dr. Cetaruk obtained a medical degree from the New York University School of Medicine in 1991. He became a fellow of the American College of Medical Toxicology in 2009. Exhibit O (Dr. Cetaruk's curriculum vitae).

The focus of Dr. Cetaruk's work in this case was to respond to Dr. Steinman's theories of causation, especially the theory that alum can harm the recipient of a vaccine. See Tr. 593. Because the details of Dr. Steinman's alum theory are not an issue on remand, it is not necessary to evaluate the depths of Dr. Cetaruk's background.

Other special masters have commented on Dr. Cetaruk's detail-oriented approach to his reports and testimony. Specifically, in addition to providing

"much greater detail in his reports" than the opposing experts, he "more coherently and effectively communicated the basis for [his] opinions." Bushnell v. Sec'y of Health & Human Servs., No. 02-1648V, 2015 WL 4099824, at *15 (Fed. Cl. Spec. Mstr. June 12, 2015). He also is not reticent to critique or strongly disagree with opposing experts' theories or contentions. See Rogero v. Sec'y of Health & Human Servs., No. 11-770V, 2017 WL 4277580, at *53 (Fed. Cl. Spec. Mstr. Sept. 1, 2017), mot. for rev. denied, slip op. (Fed. Cl. Jan. 11, 2018), aff'd, 748 F. App'x 996 (2018), petition for cert. denied, 140 S. Ct. 378, 205 (2019), petition for reh'g denied, 140 S. Ct. 656 (2019); see also Hooker v. Sec'y of Health & Human Servs., No. 02-472V, 2016 WL 3456435, at *36 (Fed. Cl. Spec. Mstr. May 19, 2016) ("Respondent's expert medical toxicologist, Dr. Cetaruk, was highly persuasive in his detailed critique of Dr. Haley's theory.").

4. Dean Jones

Professor Jones received his Ph.D. from the Oregon Health Sciences University in 1976. While he is not a medical doctor, the Emory University School of Medicine appointed him to be a professor in the department of medicine in 2003. Exhibit L (Professor Jones's curriculum vitae).

Professor Jones is an expert in the field of oxidative stress. Tr. 633. In this case, his task was to evaluate Dr. Niyazov's theory that vaccines caused Trystan oxidative stress and this oxidative stress harmed Trystan. Professor Jones did not find support for this theory. Tr. 646, 659. However, like Dr. Cetaruk's opinions regarding alum, Professor Jones's opinions about oxidative stress are outside the scope of the remand order.

Other special masters have commented on Professor Jones's cohesive testimony. He has "testified knowledgeably and understandably." Mead v. Sec'y of Health & Human Servs., No. 03-215V, 2010 WL 892248, at *9 (Fed. Cl. Spec. Mstr. Mar. 12, 2010). He is also thought to be "logical" in the presentation of his theories and opinions. Dwyer v. Sec'y of Health & Human Servs., No. 03-1202V, 2010 WL 892250, at *115 (Fed. Cl. Spec. Mstr. Mar. 12, 2010). This is particularly with respect to his expertise in the concept of oxidative stress—an area in which his testimony has been considered very persuasive in past cases. See Bast v. Sec'y of Health & Human Servs., No. 01-565V, 2012 WL 6858040, at *5 (Fed. Cl. Spec. Mstr. Dec. 20, 2012), mot. for rev. denied sub. nom., M.S.B. v. Sec'y of Health & Human Servs., 117 Fed. Cl. 104 (2014), app. dismissed, 579 F. App'x 1001 (Fed. Cir. 2014); Dwyer, 2010 WL 892250, at *115.

The backgrounds of the experts, particularly Doctors Steinman, Niyazov, and Raymond, contribute to the resolution of this case.

IV. Standards for Adjudication

Petitioners are required to establish their case by a preponderance of the evidence. 42 U.S.C. § 300aa–13(1)(a). The preponderance of the evidence standard requires a "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010) (citations omitted). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing special master's decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357 (Fed. Cir. 2000); Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty).

Petitioners bear a burden "to show by preponderant evidence that the vaccination brought about [the vaccinee's] injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

The Althen prongs are reviewed in the sections that follow. Because the medical theory is foundational to the claim that the DTaP vaccine harmed Trystan, the medical theory (prong 1) is reviewed first in section V. The medical theory, in turn, is the basis for determining the time for which an adverse reaction to the DTaP vaccine is expected to occur. Thus, section VI addresses the appropriate temporal relationship. As briefly explained at the end of section VI, the Sanchezes have not persuasively demonstrated that Trystan's neurologic problem developed within the expected time. Thus, the Sanchezes do not meet their burden of proof regarding prong 3. Section VII expands upon when Trystan began to manifest neurologic problems by reviewing in detail the medical records to show that the

Sanchezes have not established a logical sequence of cause and effect between the vaccination and Trystan's Leigh's syndrome.

V. Althen Prong 1

On remand, the parties dispute whether the remand allows for a re-adjudication of the evidence as to whether the DTaP vaccine can cause neurodegeneration as part of Leigh's syndrome. Because of the procedural posture, the remand does not permit another examination of this evidence.

A. Procedural History regarding Prong 1

The October 9, 2018 decision found the Sanchezes met their burden regarding prong 1. The decision states:

> To demonstrate that vaccinations can cause the onset of Leigh's syndrome, the Sanchezes provide evidence showing that the onset of Leigh's syndrome is associated with a *decompensating event*[10] and that vaccination could cause such a decompensating event. Though a link between vaccination and the onset of Leigh's syndrome has not been established to the standard of medical certainty, for the reasons elucidated below, the evidence presented is sufficient to conclude that the Sanchezes' theory is plausible insofar as it is consistent with contemporary understanding of the biological systems at play. Accordingly, the Sanchezes have met their statutory burden on this element as the Federal Circuit has defined it. See Hibbard v. Sec'y of Health and Human Servs., 698 F.3d 1355, 1365 (Fed. Cir. 2012) (noting that petitioners' burden is to provide a "viable medical theory by which a vaccine can cause the injury claimed by the petitioner").

Decision at 18, 2018 WL 5856556, at *11.

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[10] Decompensation is a period of regression that is frequently seen in cases of Leigh's disease. Exhibit 148 (Rahman) at 1. Dr. Raymond testified that decompensation in individuals with Leigh's syndrome is clinically obvious and is characterized by encephalopathy, decreased consciousness, weakness, and motor difficulties. Tr. 794-95. Dr. Niyazov largely agreed with this characterization of decompensation but noted that the decompensation can be followed by periods of prolonged stabilization and possibly even improvement. See Tr. 417.

For a special master to find that a petitioner has met his burden with respect to prong 1, a petitioner must provide a persuasive – not merely a "plausible" – medical theory connecting the vaccine to the alleged injury. See Boatmon v. Sec'y of Health & Human Servs., 941 F.3d 1351, 1357 (Fed. Cir. 2019). The Federal Circuit has established and reaffirmed the insufficiency of the "plausibility" standard in multiple cases. See LaLonde v. Sec'y of Health & Human Servs., 746 F.3d 1334, 1339 (Fed. Cir. 2014) ("[S]imply identifying a 'plausible' theory of causation is insufficient for a petitioner to meet her burden of proof."); Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 (Fed. Cir. 2010) (rejecting "proof of a 'plausible' or 'possible' causal link between the vaccine and injury" as the applicable statutory standard); see also Boatmon, 941 F.3d at 1360 ("We have consistently rejected theories that the vaccine only 'likely caused' the injury and reiterated that a 'plausible' or 'possible' causal theory does not satisfy the standard.").

Before the Court of Federal Claims and the Federal Circuit, the Secretary argued that the undersigned evaluated the evidence according to the wrong evidentiary standard. Resp't's Resp. to Mot. for Rev. at 9 n.10; Br. of Appellee-Respondent at 16 n.5. In both briefs, the Secretary presented this argument in footnotes and contended that given the findings on the other Althen prongs, any error was "harmless."

The Federal Circuit appeared to endorse the theory that vaccines can cause fever and fever can cause neurodegeneration based upon its opinion in Paluck.[11] Specifically, the Federal Circuit stated that "as in this case, the evidence in Paluck showed that vaccines can activate the immune system, which in an individual with a mitochondrial disease can result in oxidative stress that can, in turn, cause progressive neurological deterioration over time." Sanchez, 809 F. App'x at 851 (citing Paluck, 786 F.3d at 1380-81).

[11] The degree to which Paluck, itself, made findings regarding this theory has been questioned. See Reed v. Sec'y of Health & Human Servs., No. 08-650V, 2018 WL 6844458, at *90 n.150 (Fed. Cl. Spec. Mstr. Dec. 4, 2018); Pope v. Sec'y of Health & Human Servs., No. 14-078V, 2017 WL 2460503, at *11 (Fed. Cl. Spec. Mstr. May 1, 2017) (noting that the Secretary did not challenge prong 1 after the first remand); H.L. v. Sec'y of Health & Human Servs., No. 10-0197V, 2016 WL 3751848, at *14-15 (Fed. Cl. Spec. Mstr. Mar. 17, 2016), mot. for rev. denied, 129 Fed. Cl. 165 (2016), aff'd, 715 F. App'x 990 (Fed. Cir. 2017).

B. Arguments on Remand regarding Prong 1

The undersigned directed the parties to address whether evaluation of prong 1 was required. Order, issued July 10, 2020. In response, the Secretary maintained that nothing precludes a further analysis. Resp't's Remand Br. at 19. The Secretary did not discuss either the law of the case doctrine or the mandate rule in this context.

The Sanchezes' initial brief was similarly undeveloped. Also without citing any authority, the Sanchezes maintained that reevaluation of prong 1 is precluded. Pet'rs' Remand Br. at 85. But, the Sanchezes expanded those arguments in reply.[12] They contended that noting an objection does not elevate an appellate issue and the Secretary did not file his own appeal regarding prong 1. Thus, in the Sanchezes' view, the lack of appellate pursuit of this issue by the Secretary amounts to a waiver of any argument. Pet'rs' Reply on Remand at 23-24.

C. Resolution

Preliminarily, the Sanchezes' suggestion that the Secretary was required to file an appeal appears misplaced. See Aventis Pharma S.A. v. Hospira, Inc., 637 F.3d 1341 (Fed. Cir. 2011) (granting motion to strike a cross-appeal that did not seek to expand the putative cross-appellant's rights under the judgment). However, the Sanchezes' comments regarding how the Secretary presented his "harmless error" argument---in a footnote to the Federal Circuit---may be more meaningful. See SmithKline Beecham Corp. v. Apotex Corp., 439 F.3d 1312, 1320 (Fed. Cir. 2006) (explaining an argument needs to be developed, not just in a footnote). Regardless, the undersigned trusts that the Federal Circuit considered the Secretary's arguments regarding prong 1. See Allapattah Services, Inc. v. Exxon Corp., 372 F. Supp. 2d 1344, 1364 (S.D. Fla. 2005) ("This Court will not presume that the Circuit panel completely disregarded an argument specifically raised on appeal"). Furthermore, the doctrine of the law of the case, which precludes relitigation of issues explicitly *or implicitly* decided on appeal, sheds light on implicit appellate considerations of arguments. See Travelers Ins. Co. v. United States, 72 Fed. Cl. 316, 325 (2006) ("The doctrine [of the law of the case], of course does not constrain a trial court's consideration of an issue that has not been considered on appeal. [] But the doctrine extends to issues that were implicitly addressed." (citing W.L. Gore & Assocs., Inc. v. Garlock, Inc., 842 F.2d

[12] The Secretary's reply did not address the mandate rule in the context of prong 1.

1275, 1278 (Fed. Cir. 1988) ("The doctrine [of the law of the case] applies not only to issues discussed and decided but also those decided by necessary implication."))); American Satellite Co. v. United States, 34 Fed. Cl. 468, 480 (1995) ("Although the opinion issued by the Federal Circuit did not address the waiver question . . . further consideration of this issue is precluded by the appellate decision. . . . [T]he law of the case doctrine applies to issues implicitly decided by the appellate court.").

"Upon return of its mandate, the district court cannot give relief beyond the scope of that mandate, but it may act on matters left open by the mandate." Laitram Corp. v. NEC Corp., 115 F.3d 947, 951 (Fed. Cir. 1997) (quoting Caldwell v. Puget Sound Elec. Apprenticeship & Training Tr., 824 F.2d 765, 767 (9th Cir. 1987)) (internal quotation marks omitted). Here, the Federal Circuit's mandate does not indicate that the undersigned should reconsider the findings regarding prong 1 in the October 9, 2018 decision. Indeed, if anything, the Federal Circuit seems to be agreeing with the outcome reached in the October 9, 2018 decision on prong 1.

Accordingly, the finding in the October 9, 2018 decision remains undisturbed. The theory that the DTaP vaccine can cause neurodegeneration, potentially through the intermediate step of a fever, is sound and reliable under prong 1.

VI. Althen Prong 3

"[T]he proximate temporal relationship prong requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." de Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008). Thus, the third prong of Althen implicitly has two parts. A petitioner must show the "timeframe for which it is medically acceptable to infer causation" and that the onset of the disease occurred in this period. Shapiro v. Sec'y of Health & Human Servs., 101 Fed. Cl. 532, 542-43 (2011), recons. denied after remand on other grounds, 105 Fed. Cl. 353 (2012), aff'd without op., 503 F. App'x 952 (Fed. Cir. 2013).

As explained in section A, below, the parties have disputed both parts of prong 3. Thus, the procedural history of the parties' arguments on prong 3 are set forth in detail. The procedural history shows that the appropriate temporal relationship that was found in the October 9, 2018 decision was not disturbed on appeal. For reasons described in section B, below, this remand decision again

finds the same appropriate temporal relationship between a vaccination and the onset of neurologic deterioration.

A. Procedural History regarding Prong 3

The October 9, 2018 decision discussed evidence regarding the appropriate timing between a decompensating event and the onset of neurologic symptoms, including Edmonds (exhibit 75), Shoffner (exhibit 86), and the Poling case report (exhibit 54). See Joseph L. Edmonds et al., *The Otolaryngological Manifestations of Mitochondrial Disease and the Risk of Neurodegeneration With Infection*, 128 Arch Otolaryngol Head Neck Surg. 355 (2002), filed as exhibit 75; John Shoffner et al., *Fever Plus Mitochondrial Disease Could Be Risk Factors for Autistic Regression*, 254 J. Child Neurology 429 (2010), filed as exhibit 86; Jon S. Poling et al., *Developmental Regression and Mitochondrial Dysfunction in a Child With Autism*, 21 J. Child Neurology 170 (2006), filed as exhibit H-15. While these articles "are far from comprehensive," they suggested that neurodegeneration would occur within approximately two weeks. Decision at 26, 2018 WL 5856556, at *16. However, the October 9, 2018 decision attempted to avoid setting a "hard and fast deadline," which would conflict with the dictate in Paluck, 786 F.3d at 1383. Accordingly, the October 9, 2018 decision did not specify the outside time frame at which neurodegeneration could appropriately be linked to an antecedent event. But, the October 9, 2018 decision found that the Sanchezes failed to establish that they were entitled to compensation because of (a) the length of time between the February 5, 2009 vaccination and the onset of Trystan's neurodegeneration, which started no earlier than May 1, 2009 (almost three months later), and (b) infections that Trystan suffered much closer in time to the onset of his neurodegeneration.

In their motion for review, the Sanchezes challenged the evaluation of the appropriate temporal relationship.[13] The Sanchezes argued that the October 9, 2018 decision violated Paluck, interpreted the Edmonds article incorrectly, and ignored (or overlooked) the testimony of Dr. Niyazov that a fade response could extend the appropriate temporal relationship out to two or three months. Pet'rs' Mot. for Rev. at 20-25. In reply, the Sanchezes added an argument that the

[13] This aspect of the Sanchezes' argument corresponds to the first part of Althen prong 3. The Sanchezes also presented arguments about the second part of Althen prong 3, when Trystan began to suffer neurodegeneration. Those are addressed in sections VI.B & VI.C below.

October 9, 2018 decision conflicted with Paluck in that the undersigned relied upon small studies.

In denying the Sanchezes' motion for review, the Court of Federal Claims rejected the Sanchezes' arguments. In particular, the Court of Federal Claims ruled that the undersigned did not violate Paluck because the decision did not set a hard and fast deadline. The Court further ruled that the special master did not have to accept the Sanchezes' argument that the appropriate temporal relationship could extend to two or three months. Opinion and Order at 255-56.

On appeal to the Federal Circuit, the parties' arguments with respect to the appropriate temporal relationship largely, if not entirely, matched their arguments to the Court of Federal Claims. For example, the Sanchezes again argued that the special master ignored Dr. Niyazov's testimony about the Naviaux article. The Sanchezes also argued that the October 9, 2018 decision erroneously set a hard and fast deadline, in violation of Paluck.

In disagreement with the Sanchezes' arguments, the Federal Circuit ruled that the decision was in accord with Paluck. The Federal Circuit did not comment upon the usefulness of the Naviaux article. However, the Federal Circuit remanded for a separate analysis of prong 2 and prong 3. The Federal Circuit required that the undersigned find whether Trystan's February 16, 2009 arm contortions could contribute to finding that the Sanchezes met their burden with respect to Althen prong 3.

On remand, the parties were instructed to present arguments regarding both parts of Althen prong 3. Order, issued July 10, 2020. For the temporal interval for which an inference of causation is appropriate (part 1), the parties appeared to struggle to set any bounds. Copying from their July 7, 2017 pre-hearing brief, the Sanchezes argued that neurodegeneration would often occur within two weeks, possibly three weeks after the inciting event. Pet'rs' Remand Br. at 53-64. The Secretary did not specify an appropriate amount of time, other than to maintain that "several months" is too long. Resp't's Remand Br. at 20. In reply, the Sanchezes presented very little, if anything, about the appropriate temporal relationship. See Pet'rs' Remand Reply at 10-14 (discussing prong 2).

B. Analysis of Althen Prong 3, part One

At its foundation, Althen requires "a showing of a proximate temporal relationship between vaccination and injury." 418 F.3d at 1278. Subsequent Federal Circuit cases have developed aspects of this element. For example,

Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1358 (Fed. Cir. 2006), explained "[i]f, for example, symptoms normally first occur ten days after inoculation but petitioner's symptoms first occur several weeks after inoculation, then it is doubtful the vaccination is to blame." Id. de Bazan linked the medically acceptable timeframe to the "medical understanding of [a] disorder's etiology." de Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008). In accord with these precedents, special masters may reject an opinion that is so indefinite about the appropriate temporal relationship that the opinion would effectively render the third Althen prong a nullity. Hennessey v. Sec'y of Health & Human Servs., 91 Fed. Cl. 126, 141-42 (2010). Similarly, special masters may find that when the onset of a disease occurs outside the expected temporal interval, petitioners are not entitled to compensation. Greene v. Sec'y of Health & Human Servs., No. 11-631V, 2019 WL 4072110, at *21 (Fed. Cl. Spec. Mstr. Aug. 2, 2019), mot. for rev. denied, 146 Fed. Cl. 655 (2020).

While those cases suggest that sometimes the interval between the vaccination and the onset of symptoms is too long to support a finding of causation-in-fact, Paluck cautions against defining the limits too rigidly. With this guidance, the undersigned attempted to point out that the evidence, imperfect as it might be, seemed to coalesce around a finding that two weeks from vaccination to the onset of neurologic decline is an interval that would support a finding of causation.[14] Decision at 25, 2018 WL 5856556, at *15. Yet, at the same time, the undersigned tried to balance what the evidence showed with Paluck's recognition

[14] The Sanchezes' criticism that the undersigned erred in relying upon small studies, see Pet'rs' Reply in Support of Mot. for Rev. at 11-12; see also Pet'rs' Mot. for Rev. at 31 (highlighting the portion of Paluck that identifies the Shoffner and Edmonds articles, and Poling case study, as not establishing a definitive time frame due in part to small patient sample sizes); Pet'rs' Remand Br. at 63 (same), seems misplaced in that the *Sanchezes* introduced the studies, such as Edmonds and Shoffner, on which the undersigned relied. Special masters have commented that they base decisions on studies with small samples because "[e]vidence from small studies may be the only evidence available to support or undercut an opinion on causation." Holt v. Sec'y of Health & Human Servs., No. 05-0136V, 2015 WL 4381588, at *30 n.84 (Fed. Cl. Spec. Mstr. June 24, 2015); see also H.L. v. Sec'y of Health & Human Servs., No. 10-0197V, 2016 WL 3751848, at *11 (Fed. Cl. Spec. Mstr. Mar. 17, 2016) ("[T]he Edmonds study remains the *only* evidence in this record regarding the expected timing of a neurologic deterioration[.]"), mot. for rev. denied, 129 Fed. Cl. 165, 175-76 (2016) (rejecting argument that special master erroneously relied upon Edmonds), aff'd, 715 F. App'x 990, 997 (Fed. Cir. 2017) ("The special master's 'requirement for strong temporal evidence' in this regard does not contravene Paluck and is 'consistent with the third prong of the Althen test.'").

that more studies would be helpful. Cf. Sharpe v. Sec'y of Health & Human Servs., 964 F.3d 1072, 1083 (Fed. Cir. 2020) (criticizing special master for noting that different evidence could lead to a different result).

On appeal, the Federal Circuit did not correct this approach. Because the mandate does not remand for reconsideration of the first part of Althen prong 3, the undersigned will again *primarily* look for evidence of neurologic decline within two weeks of the vaccination. However, if Trystan's neurologic decline were to occur slightly outside of two weeks, then the Sanchezes could meet their burden regarding Althen prong 3.[15]

C. Analysis of Althen Prong 3, part Two

The ensuing question, a topic of the Federal Circuit's remand, is whether the Sanchezes presented persuasive evidence that Trystan began to suffer lasting neurologic problems within approximately two weeks of the vaccination.[16] The short answer is that the Sanchezes have not. When the record is considered as a whole, the symptoms that Trystan displayed on February 5, 2009, as well as on February 15-16, 2009, including his arm contortions, are not manifestations of a neurologic disorder. The longer answer and more detailed explanation are provided as part of the prong 2 analysis below.

VII. Althen Prong 2

On remand, the procedural history of the arguments regarding prong 2, which is set out in section A, again complicate the issues. A chief question is when Trystan started to experience neurodegeneration because if, as the Sanchezes' theory predicts, Trystan developed neurodegeneration within a short time (approximately two weeks) after the vaccination, then a "logical" conclusion might be that the vaccination caused the neurodegeneration. This argument is

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[15] Even if the Federal Circuit remanded the question of Althen prong 3, part 1, the undersigned would still find that the evidence weighs in favor of finding that neurodegeneration would occur within approximately two weeks from an allegedly inciting event. Even Naviaux indicates that the fade response is "typically delayed two to ten days after a fever." Tr. 438 (Dr. Steinman).

[16] The qualification of "lasting" problems refers to the requirement that petitioners must establish that an injury persisted longer than six months. 42 U.S.C. § 300aa-11(c)(1)(D). As such, while the vaccination caused Trystan to have a fever and to cry inconsolably, this initial and transient reaction is not compensable.

developed in section B, which restates the theory the Sanchezes and their experts advance. Section B also includes a detailed analysis of Trystan's health at various times, corresponding to visits to medical providers. Section B ultimately presents the finding that Trystan's neurodegeneration began later than the time predicted by the Sanchezes' theory. Within this section on the logical sequence of cause and effect (section V), there is an analysis of reports from doctors who treated Trystan because the reports of treaters may influence the outcome on prong 2.

A. Procedural History regarding Logical Sequence of Cause and Effect / Onset of Neurodegeneration

As discussed above with respect to prong 3, the October 9, 2018 decision found that the Sanchezes failed to establish that the DTaP vaccination caused Trystan's neurologic problems because Trystan lost skills no earlier than May or June 2009, which was too long after the February 5, 2009 vaccination to infer causation-in-fact and because Trystan suffered infections in April and May. Decision at 22-24, 2018 WL 5856556, at *13-15.

In their motion for review, the Sanchezes argued that the undersigned was arbitrary in that the October 9, 2018 decision failed to address their position that the neurodegeneration began immediately after the February 5, 2009 vaccination when Trystan had a fever, inconsolable crying, and a hot spot on his leg. Pet'rs' Mot. for Rev. at 32. Specifically, the Sanchezes argued that the undersigned did not adequately address Dr. Steinman's and Dr. Niyazov's contentions that "fever, irritability, and other signs" were indicators of the onset of neurodegeneration as part of a development process that does not adhere to a "rigid timeframe for when the clinical symptoms of vaccine-induced neurodegeneration would be expected to appear." Id. Similarly, in their motion, the Sanchezes added that the undersigned improperly ignored evidence that Trystan faded after the vaccination. See id. at 10.

The Court did not accept the Sanchezes' arguments. The Court ruled that the Sanchezes were suggesting that the undersigned wrongly weighed evidence regarding the onset of neurodegeneration. The Court, accordingly, determined that such an argument about re-weighing evidence was not acceptable and denied the motion for review on this point. Opinion and Order at 254.

At the Federal Circuit, the Sanchezes returned to the issue of when Trystan's neurodegeneration began. The opening section of their initial brief as well as the opening section of their reply brief is devoted to the topic of the onset of neurodegeneration. Br. of Appellants-Petitioners at 4; Reply of Appellants-

Petitioners at 1. They argued that Trystan's crying and fever marked the beginning of his neurodegeneration. Br. of Appellants-Petitioners at 34; Reply of Appellants-Petitioners at 7. They also compared Trystan to the children in Markovich and Paluck.

The Federal Circuit did not directly address whether Trystan's fever and crying from the day and evening after the February 5, 2009 vaccination constituted a manifestation of neurodegeneration. However, the Federal Circuit remanded for consideration of whether Trystan's February 16, 2009 arm contortions were a manifestation of a neurological injury. Sanchez, 809 F. App'x at 853.

On remand, the Sanchezes' position with respect to onset is not thoroughly consistent. The Sanchezes primarily advance the position that Trystan's fever and inconsolable crying on February 5, 2009, were the first manifestation of his neurologic injury. Pet'rs' Remand Br. at 42. They fault the October 9, 2018 decision for not addressing their claim that Trystan's fever, irritability, and potential encephalopathy are the onset of his neurologic disorder. Id. at 49. They go so far as to argue that the undersigned's Remand Decision must address the fever, inconsolable crying, and arm contortions. Id. at 51. However, by quoting Dr. Steinman's June 15, 2020 report, the Sanchezes also state that the February 16, 2019 arm contortions are "evidence of the onset of neurodegeneration." Id. at 13-14 (quoting exhibit 185).

The Secretary's argument with respect to Trystan's onset of neurologic problems focuses on Trystan's behavior on February 16, 2009. The Secretary appears not to address Trystan's behavior on February 5, 2009. Resp't's Remand Br. at 19-21; see also Br. of Appellee-Respondent at 17, 24 (attributing all Trystan's problems in February 2009 to a cold).

In the sections that follow, the undersigned will address Trystan's neurologic status at different periods, including February 5, 2009; February 16-17, 2009; the end of February through early April 2009; April-May 2009; August 2009; and October-December 2009. As part of the final section (October-December 2009), the undersigned will discuss challenge-rechallenge. The undersigned will also address the contributions of treating doctors in this case and evaluate their relevance and weight in analyzing the Sanchezes' claim. But, the analysis of Althen prong 2 begins with a recapitulation of the Sanchezes' theory of how the DTaP vaccine can harm Trystan.

B. Summary of Causal Theory

The second element in Althen's formulation of elements to establish causation-in-fact is "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." Althen, 418 F.3d at 1278. A "logical" sequence suggests that the vaccinee responded in a way consistent with the causal theory. For example, when a petitioner presents a theory that a vaccine can attack the autonomic nerves, the special master may find against the petitioner due to the lack of preponderant evidence showing an autonomic neuropathy. Hibbard v. Sec'y of Health & Human Servs., 698 F.3d 1355, 1364 (Fed. Cir. 2012); see also Dodd v. Sec'y of Health & Human Servs., 114 Fed. Cl. 43, 54 (2013) ("Petitioner's argument fails because . . . the Chief Special Master tested the proposed mechanism of causation . . . and found that the proposed mechanism, as applied to the facts of S.S.'s seizures . . . failed to provide a logical sequence of cause and effect."); La Londe v. Sec'y of Health & Human Servs., 110 Fed. Cl. 184, 205 (2013) (affirming a special master's determination that the non-existence of an asserted condition constituted a "missing link" in the Althen prong 2 causation analysis), aff'd, 746 F.3d 1334 (Fed. Cir. 2014). Thus, a petitioner's causal theory affects whether the evidence offered in an attempt to show "that the vaccination was the reason for the injury" is "logical."

Here, through opinions of their experts and arguments of their attorney, the Sanchezes maintain that Trystan's response to the vaccine changed his life. After the vaccination, Trystan started "a downward cascade." Tr. 278 (Dr. Steinman). Dr. Steinman confirmed his opinion in his testimony on remand. Tr. 2033-34. He saw Trystan's deterioration as "one continuous process", Tr. 294, and "evolving in a continuum," Tr. 296-97. "[T]he dynamic effect of the shot was to create damage in the nervous system which, as the child developed, became apparent at different points with losing skills and other manifestations." Tr. 295. Dr. Steinman further stated that, while there are various reasons a child's loss of skills may be subtle, at a certain point in Trystan's medical history, doctors began noting concrete and serious loss of milestones, which "didn't happen overnight." Tr. 296. On remand, Dr. Steinman characterized Trystan as taking a "big hit" in February. Tr. 2042.

Dr. Niyazov wrote that Trystan's "developmental regression was slowly developing ever since the crying and fever took place as a result of the vaccination." Exhibit 68 at 8. Dr. Niyazov testified that the vaccination and its associated inflammation took energy from Trystan from which he could not recover for two to three months. Tr. 415-16. Dr. Niyazov testified that Trystan's

Leigh's syndrome started with the fever and inconsolable crying on February 5, 2009. Tr. 457.[17]

In addition to presenting this testimony from their experts, the Sanchezes analogize their case to two cases, Markovich and Paluck, which reached the Federal Circuit. They also compare their case to Poling. Thus, a review of the facts in those cases is appropriate.

Markovich

Ashlyn Markovich received a set of vaccinations, including the DTaP vaccine, on July 10, 2000. Markovich v. Sec'y of Health & Human Servs., No. 03-2015V, 2005 WL 6117470, at *1 (Fed. Cl. Spec. Mstr. July 22, 2005). Later that day, Ashlyn started to blink her eyes "repeated[ly]." Id. Supported by an affidavit, the petition alleged that "after Ashlyn's July 10, 2000 vaccinations and continuing to August 30, 2000, the parents observed Ashlyn rapidly blinking her eyes." Id. A pediatric neurologist who testified for the petitioners, Jean-Ronel Corbier, accepted the assertions contained in the affidavit. Dr. Corbier opined that "[T]here is a possibility that these rapid frequent eye blinking episodes may have represented seizures." Id. at *1 n.9. Another doctor, Donald H. Marks, opined that the DTaP vaccination caused the development of the seizure disorder. Id. at *1 n.8. "Ashlyn's first full-blown seizure . . . occur[ed] [on] August 30 or 31, 2000." Id. at *1.

To determine whether the petition, which was filed on August 29, 2003, was filed within the three-year statute of limitations, the special master held a hearing during which the only person to testify was Dr. Corbier. Id. at *2. "Dr. Corbier explained that although rapid eye blinking alone is insufficient to establish a seizure disorder diagnosis, as a neurologist, the eye blinking episode would have raised his suspicions and he would have pursued further investigation[.]" Id. at *11. Dr. Corbier also made "plain that the eye blinking episodes were part of a progression of symptoms." Id. In opining that the July 10, 2000 DTaP vaccination

[17] Later, on remand, Dr. Niyazov stated that this testimony was not accurate. Dr. Niyazov stated that Trystan's Leigh's syndrome began on December 15, 2009, when he underwent an MRI, because an MRI is only mechanism by which Leigh's syndrome could be diagnosed. Tr. 2072-73. He stated that he may have misspoke at the original entitlement hearing by making "a common error where when people sometimes have interchangeable use of the words mitochondrial complex II deficiency and Leigh's disease." Id. 2072. This remand testimony from Dr. Niyazov was confusing and not persuasive.

caused the August 30, 2000 seizure, "Dr. Corbier explained that if there had been no evidence of brain dysfunction between July 10, 2000, and August 30, 2000, it would be more difficult to prove that the vaccinations Ashlyn received on July 10, 2000, were the cause of her seizure disorder." Id. at *13.

Dr. Corbier's opinion about the significance of the eye blinking episodes was "critical to the special master's decision." Id. The special master found that because Ashlyn manifested some neurologic problem on July 10, 2000, the statute of limitations began to run on that day. The special master rejected the petitioners' arguments that because they did not recognize until later the significance of the eye blinking episodes, the statute of limitations should not start running until August 30, 2000. Id. at *14. Therefore, despite sympathy for the Markoviches, the special master found that the statute of limitations barred the petition.[18]

In the present case, the Sanchezes compare Trystan to Ashlyn. To the Sanchezes, Trystan's "fever, hot spot, and inconsolable crying" are the onset of his neurological disorder just as Ashlyn's eye blinking marked a manifestation of her seizure disorder. To continue the analogy, the Sanchezes state Trystan's "loss of skills in May 2009 is similar to the grand mal seizure." Pet'rs' Remand Br. at 43.

However, Trystan and Ashlyn differ. The differences are apparent in at least two ways. First, in Markovich, Dr. Corbier accepted the parental account that Ashlyn had repeated and frequent episodes of eye blinking between the day of vaccination and the August 30, 2000 seizure. The numerous instances allowed Dr. Corbier to see a "progression of symptoms."[19] In contrast, Trystan did not display any neurologic problems for weeks after the February 16, 2009 incident.

Second, in Markovich, Dr. Corbier's opinion that the eye blinking constituted a manifestation of a neurologic disorder was unopposed. Here, while Dr. Steinman and Dr. Niyazov maintain that Trystan's neurodegeneration began on

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[18] The Court of Federal Claims ruled that the special master's reliance on Dr. Corbier's testimony was not arbitrary and denied the petitioners' motion for review. 69 Fed. Cl. 327 (2005). The Federal Circuit affirmed. 477 F.3d 1353 (Fed. Cir. 2007).

[19] In evaluating the motion to dismiss for failure to file within the time the statute of limitations permits, the special master seemed to accept the reliability of the affidavit. The Secretary, however, noted that "there is no mention in the medical records of Ashlyn's eye fluttering." Markovich, 2005 WL 6117470, at *2.

February 5, 2009, Dr. Raymond opposes this opinion. This point is developed further below.

Paluck

The Sanchezes often compare their case to Paluck. See, e.g., Pet'rs' Pre-hear'g Br., filed July 7, 2017, at 17-19, 46-50; Pet'rs' Mot. for Rev., filed Nov. 8, 2018, at 20-32; Br. of Appellants-Petitioners at 18-19, 23, 28, 35-48; Pet'rs' Remand Br. at 61-64. Therefore, a brief (not exhaustive) review of the facts of Paluck is appropriate.

The vaccinee in Paluck was a child named Karl Paluck. He most likely was born with a mitochondrial disorder. Paluck v. Sec'y of Health & Human Servs., 113 Fed. Cl. 210, 213 (2013), aff'd, 786 F.3d 1373 (Fed. Cir. 2015). Before vaccinations around his first birthday in January 2005, Karl was diagnosed with developmental delays in various domains. Id. at 214. Within two days of the vaccinations, his daycare provider documented that Karl was running a fever, was irritable, and had fatigue. Id. at 216. Within the next two weeks, Karl "was often fussy, did not eat or nap well, and was tired." Id. at 217.

About three weeks after vaccination, Karl's parents brought him to a chiropractor because Karl was having problems sitting, crawling, and walking. Id. Over the next two months, the chiropractor recorded a series of variable subjective assessments about Karl's abilities. Id.

By April 2005, Karl's pediatrician and a pediatric neurologist to whom Karl had been referred were identifying worse problems with Karl. In short, Karl was experiencing "global delayed development." Id. at 218. He further deteriorated from April to July. Id. at 219. In July, Karl had a seizure and an MRI suggested that Karl was suffering from neurodegeneration. Id.

The Court found that the Palucks' case should be analyzed as a significant aggravation case, not a new injury case. Id. at 228. The Court then applied the six elements from Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009).

With respect to the sixth Loving factor, which corresponds to Althen prong 3, the Court declined to set "a hard and fast time frame" for which a vaccination would aggravate a mitochondrial disorder. Paluck, 113 Fed. Cl. at 240. Nevertheless, the Court recognized that, at a minimum, the experts agreed that a change would begin "within a few weeks." Id. (quoting testimony from the

Secretary's expert). The experts' opinions derived, in part, from the Edmonds article, the Shoffner study, and the Naviaux commentary on the Shoffner study.

The Court found that the Palucks had established their burden of showing that Karl experienced neurodegeneration within this period. The Court credited the testimony of the Palucks' expert who relied upon a relatively early notation by the chiropractor that Karl was "spastic" on February 11, 2005. According to the Court, "[s]tarting with this chiropractic notation, the record shows that Karl experienced a general decline." Id. Karl exhibited various issues continually before and after vaccination, including developmental delays, bouts of otitis media and erythema multiforme, neuromuscular issues, global developmental delay, and skin lesions. Id. at 213-18.

Poling

Through Dr. Niyazov, the Sanchezes have compared Trystan to Hannah Poling. See Pet'rs' Pre-hear'g Br., filed July 7, 2017, at 47-50; Pet'rs' Mot. for Rev., filed Nov. 8, 2018, at 26, 31; Pet'rs' Reply in Support of their Mot. for Rev. at 11-12.[20] While the Poling case carries some renown in the Vaccine Program, the events in Hannah Poling's life should be reviewed again.

At age 19 months, Hannah Poling received multiple vaccinations, including the diphtheria-tetanus-pertussis and varicella vaccines. Within 48 hours, she developed a fever, inconsolable crying, irritability, and lethargy, and refused to walk. Four days later, she could not walk up stairs normally. Over the next three months, she was "irritable and increasingly less responsive verbally, after which the patient's family noted clear autistic behaviors." Exhibit H-15 (Poling) at 170.[21]

Hannah's parents sought compensation through the Vaccine Program.[22] The Secretary conceded that the Polings were entitled to compensation because

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[20] In these contexts, the Sanchezes also rely upon the Court's citation to Poling in Paluck.

[21] The Poling case report as published in the Journal of Child Neurology appears as exhibit H-18. A manuscript version was filed as exhibit 84.

[22] Hannah's father, Dr. Jon Poling, later stated that he "should have declared [his] daughter's identity in a separate letter to [Journal of Child Neurology]." Poling 2008, filed as exhibit 118. Dr. Poling's co-authors wrote separately to indicate that "a full disclosure of the relationship of the patient to the lead author and the submission of the case to the Vaccine Adverse Event Report System and the U.S. Vaccine Injury Compensation Program should have been made to the journal prior to publication." Exhibit 118 and exhibit H-18. The editor-in-

Hannah's case met the Table's definition of encephalopathy. Poling v. Sec'y of Health & Human Servs., No. 02-1466V, 2011 WL 678559 (Fed. Cl. Spec. Mstr. Jan. 28, 2011) (awarding attorneys' fees and costs); see also R.K. v. Sec'y of Health & Human Servs., No. 03-0632V, 2015 WL 10911950, at *14-17 (Fed. Cl. Spec. Mstr. May 23, 2016) (describing Poling case), mot. for rev. denied, 125 Fed. Cl. 57 (2016), aff'd, 671 F. App'x 792 (Fed. Cir. 2016).

Comparing Trystan and Hannah is difficult. To start, because Hannah was 19 months old when she received the vaccinations, she was capable of climbing stairs, walking, and some talking. Thus, the loss of these abilities would be more noticeable to a parent. In contrast, Trystan's abilities as a six-month-old child would naturally be more limited.

Even so, Hannah's father reported to the Journal of Child Neurology that Hannah's abilities deteriorated in the three months after vaccination. In this time, she became "increasingly less responsive verbally." Within the first few weeks after receiving her vaccination, Hannah experienced episodes of opistho-tonus whereby she would not be able to walk up stairs normally, low-grade intermittent fever, and generalized erythematous muscular rash. Exhibit 84 at 2.

These examples to which the Sanchezes compare Trystan are a foundation for examining what happened to Trystan. This analysis begins with Trystan's health on the day of his vaccination.

1. February 5, 2009

Trystan was taken to his six-month well-baby checkup with Dr. Philip Brown on February 5, 2009. Exhibit 1 at 44. Dr. Brown found his growth and development to be normal. Id. at 46. As identified by Dr. Steinman as part of his hearing testimony, normal developmental milestones for a 6-month-old include exchanging things from one hand to another, sitting, interacting, smiling, laughing, engaging, and cooing. Tr. 2052. Six-month milestones also include sitting up and supporting themselves, also referred to as a "lateral prop." Tr. 2053-54. Dr. Brown noted that Trystan was meeting his developmental milestones, including: turning to sound, self-feeding, self-comforting, responding to his name, sitting with support, grasping and mouthing objects, smiling, laughing, squealing, showing

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chief of the Journal of Child Neurology also stated that the authors should have disclosed conflict of interest. Exhibit H-18.

interest in toys, showing differential recognition of parents, babbling reciprocally, rolling over from back to front, and standing when placed. Exhibit 1 at 46. Trystan also had "no head lag when pulled to sit." Id. On this day, he received the DTaP, hepatitis B, Haemophilus influenzae type B, inactivated polio, and pneumococcal conjugate vaccines. Id. Dr. Brown recommended that Trystan return in two months to receive further vaccinations. Id.; see also Ruling Finding Facts ¶ 6.

After the wellness check with Dr. Brown, Trystan was inconsolable; he cried a loud, high-pitched cry, as if he was in pain. Tr. 18-19, 67, 177-79. He began to run a temperature of 102.2 degrees and developed a lump on his left thigh that was "really hot." Tr. 17-20, 32, 67-69, 113, 177-79. Ms. Sanchez gave Trystan Tylenol for the fever, which ebbed and flowed over the next few days. Tr. 20, 30, 68, 151, 178, 180; see also Ruling Finding Facts ¶ 6.

From this date, three facts about Trystan are the basis for much of the Sanchezes' experts' opinions. These facts are Trystan's inconsolable crying, his fever, and the hot spot on his thigh. Tr. 412, 420, 453. Of these three facts, the most important is the inconsolable crying.

Inconsolable crying can be a manifestation of an encephalopathy or injury to the nervous system. See Estep v. Sec'y of Health & Human Servs., No. 90-1062V, 1992 WL 357811, at *3 (Fed. Cl. Spec. Mstr. Nov. 3, 1992), mot. for rev. denied, 28 Fed. Cl. 664 (1993); Tr. 2020 (Dr. Steinman). Dr. Steinman, in particular, cited to the package insert for the pertussis vaccine as a way to demonstrate that Trystan's crying was a manifestation of a neurologic disorder. Tr. 257, 261, 282, 2020; see also Tr. 492 (Dr. Niyazov), 873-75 (Dr. Raymond). Dr. Raymond recognized that high-pitched crying can be compatible with an "encephalopathy," as defined in the Vaccine Injury Table. However, the high-pitched crying is not diagnostic for a Table encephalopathy. Tr. 861, 918.[23]

Inconsolable crying does not have to be a manifestation of a neurologic injury. See Cox v. Sec'y of Health & Human Servs., No. 90-1673V, 1997 WL 101594, at *1 (Fed. Cl. Spec. Mstr. Feb. 18, 1997); 42 C.F.R. § 100.3(c)(2)(i)(C)

[23] The relevant Table definition of "encephalopathy" required petitioners to establish that the vaccinee suffered, among other criteria, a loss of consciousness. 42 C.F.R. § 100.3(b)(2) (2008). Although Dr. Steinman seemed to equivocate about answering a question regarding Trystan's consciousness, Tr. 2036, Trystan did not suffer a loss of consciousness following the vaccination. Tr. 859, 869, 2119.

(2017) (stating "high-pitched and unusual screaming" does not demonstrate an "acute encephalopathy" as defined in the Vaccine Injury Table). As Dr. Steinman pointed out during the December 2017 hearing, infants sometimes cry for hours during a flight. Tr. 288. The Secretary's experts, Dr. McGeady and Dr. Raymond, testified that Trystan's inconsolable crying the day of the vaccination reflected Trystan's discomfort and pain after receiving an injection. Tr. 729-30, 762, 872, 2141.[24]

Likewise, the presence of a fever is non-specific. As the October 9, 2018 decision recognized, the experts appeared to agree that vaccines can cause an elevation in temperature and the February 5, 2009 vaccination caused Trystan's fever later that day. Tr. 412 (Dr. Niyazov).

The finding that the vaccine caused Trystan's February 5, 2009 fever, which ebbed and flowed for a few days, does not necessarily mean that Trystan experienced a prolonged abnormal reaction to the vaccine. A fever is part of the body's normal physiology. Tr. 945. Dean Jones, a leading expert on oxidative stress, stated an assertion that "fever, per se, is oxidative stress . . . is completely ludicrous." Tr. 681. Fever can be evidence of an immune response but need not be. Tr. 762 (Dr. McGeady).

Finally, the presence of a red mark on Trystan's thigh carries the least significance as even Dr. Steinman and Dr. Niyazov placed little emphasis on it.

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[24] The Sanchezes appear to overlook the distinction between their experts and the Secretary's experts about the etiology of Trystan's inconsolable crying on February 5, 2009. Dr. Niyazov associated Trystan's crying and fever with an inflammatory (or immunological) response to the vaccine. Tr. 453. Dr. McGeady associated the crying with a painful response to the vaccine. Tr. 730. It is not correct to argue that because Dr. McGeady testified that the vaccine caused Trystan's crying, Dr. McGeady has agreed with the Sanchezes' theory that the vaccine caused a lasting harm. See Pet'rs' Remand Br. at 13 (citing Tr. 728-29). Dr. McGeady merely testified as to the crying occurring as an immediate reaction, more as a co-occurrence with the immediate injection site pain commonly seen after vaccination than a lasting effect of the vaccine. See Tr. 729 ("I would not call [the red lump at the injection site] abnormal because the phenomenon is often seen in clinical pediatric practice . . . some hours later a swollen red area will develop at the injection site."); Tr. 730-31 ("Q: Do you think the inconsolable crying . . . [was] caused by the vaccine? A: I think it may very well have been. Q: And why is that? A: Well, it certainly coincided with the period when the red tender lump appeared . . . so that would fit that he was having discomfort.").

See Tr. 623 (Dr. Niyazov). But, Dr. McGeady further countered this point by saying that a red spot is not an abnormal response. Tr. 729, 752.

In short, the Sanchezes and their experts appear to place undue weight on Trystan's health on February 5-7, 2009. They seem to reason that because inconsolable crying *can be* a manifestation of an encephalopathy or injury to the nervous system, Trystan *must* have suffered a neurologic injury. See, e.g., Tr. 288; Pet'rs' Remand Br. at 44 ("Given this evidence and findings that fever and inconsolable crying are symptoms and that they 'could cause' the vaccine injury . . . then the logical conclusion is that fever, inconsolable crying and arm contortions were evidence that the neurological system had been injured and were the first onset symptoms of Trystan's vaccine injury."). But, Trystan's health could be entirely compatible with an expected response to the vaccination given in the morning of February 5, 2009.

2. February 16-17, 2009

A primary, perhaps the primary, issue for which the Federal Circuit remanded consideration was to address the significance, if any, of Trystan's behaviors February 16-17, 2009. As discussed below, Trystan's behaviors included an episode in which he contorted his arms. To address this issue, it is necessary to cover: (a) the procedural activities regarding arm contortions that have teed up this issue for consideration on remand, (b) the scope of the remand, and (c) Trystan's behaviors and health events occurring February 16-17, 2009, including their significance to the causation analysis.

a) Procedural Background concerning Arm Contortions

(1) Activities before Remand

The question about arm contortions originated at the beginning of the case. In Mr. Sanchez's October 5, 2011 affidavit, he averred that on the evening of February 16, 2009, Trystan "began to hold his arm behind his back with a lot of tension and jerk his head back. When I tried to comfort him and gently put his arm back to the normal position, Trystan would go right back to holding it behind his back again. This lasted for only a few minutes." Exhibit 4 ¶ 6. Dr. Steinman, in turn, quoted this portion of Mr. Sanchez's affidavit in opining in his first report that "in the context of a febrile illness, [Trystan] may have had a seizure." Exhibit 2 (Dr. Steinman's Sep. 28, 2011 report) at 1. Later, Dr. Steinman added that Trystan "suffered from seizures." Id. at 2.

Ms. Sanchez averred that she communicated that Trystan had "weird movements" and was "being very stiff" to Mr. Luna, the physician's assistant. Exhibit 3 ¶ 7. However, Mr. Luna's record does not memorialize any complaint about abnormal movements. See exhibit 1 at 48-51.

The discrepancy between the Sanchezes' accounts and Mr. Luna's record prompted the undersigned to hold a hearing to determine whether preponderant evidence supported a finding that Trystan, in fact, contorted his arms on the evening of February 16, 2009. After hearing testimony from the Sanchez family, the undersigned found that around February 17, 2009, "Trystan did not begin to exhibit arm contortions." Ruling Finding Facts, issued April 10, 2013, ¶ 11. The Ruling directed the parties to provide the factual findings to the experts to ensure that any expert presented opinions consistent with the factual findings. Id. at 16 (citing Burns v. Sec'y of Health & Human Servs., 3 F.3d 415, 417 (Fed. Cir. 1993)).

After some missteps, Dr. Steinman eventually offered opinions that were based upon factual assumptions consistent with the Ruling. See, e.g., exhibit 95. With this foundation, the expert witnesses testified at the December 2017 hearing. On direct examination, Dr. Steinman stated that the significance of arm contortions is "contextual" and whether it and other symptoms indicate an encephalopathic event can only be determined by employing an EEG. Tr. 257-58, 284-85. However, Dr. Steinman did include Trystan's arm contortions as part of what he considers the "continuous process" of Trystan's neurodegeneration. Tr. 298-99. Dr. Niyazov testified that arm contortions could have been one of multiple symptoms indicating "another . . . mitochondrial milestone or energy milestone in that [Trystan] decreased – he achieved a new low in his energy." Tr. 460. However, Dr. Niyazov also testified that arm contortions could be seizure activity, or "just behavioral problems that were created by the energy-starving brain." Tr. 462-63.

However, with respect to arm contortions, the October 9, 2018 decision deviated from the Ruling. This decision stated: Trystan's "arms contorted and he was jerking around." Decision at 7, 2018 WL 5856556, at *4. From this premise, the undersigned also found that Trystan's "movements were of the type typically displayed by an infant suffering from a cold." Id.

The deviation and associated reasoning were a primary ground for the Sanchezes' motion for review. The Sanchezes argued that in the undersigned's "new findings of fact, he places the arm contortions and jerking … as starting

February 15, 2009. However, [the special master] inappropriately adds his own fact that the movements were the type typically displayed by infants suffering from a cold. As previously discussed, no such evidence exists of interpreting medical symptoms by the parents or by the experts for this conclusion and thus it is arbitrary and capricious." Pet'rs' Mot. for Rev. at 29; accord id. at 4 n.5.

In response, the Secretary accepted the finding that Trystan's arms contorted. See Resp't's Resp. to Mot. for Rev. at 5 (citing both Ruling Finding Facts and Decision).[25] The Secretary defended the undersigned's conclusion that the "movements were of the type typically displayed by an infant suffering from a cold." See id. at 14-15.[26]

At the Federal Circuit, the parties repeated these arguments. The Federal Circuit ruled that because the Decision found that Trystan contorted his arms whereas the Ruling Finding Facts did not, the experts did not have an opportunity to opine on the significance, if any, of the arm contortions. The Federal Circuit rejected the Secretary's argument that his experts had linked the arm contortions to a cold. Thus, the Federal Circuit found it necessary to remand for further consideration by the experts as to the bearing that Trystan's arm contortions may have on the causation analysis.

(2) Developments regarding Arm Contortions on Remand

On remand, the parties were permitted to have their experts discuss the significance of Trystan's arm contortions. Order, issued June 12, 2020. Dr. Steinman stated that "[a]lthough the Sanchezes described it as seizures . . . , the arm contortions fall right into this definition [of dystonia]." Exhibit 185 at 2 (ellipses in original). Dr. Steinman also indicated that "[t]he arm contortions (dystonia) are not a manifestation of the common cold. I searched various websites on this matter and came up with no evidence whatsoever." Id. at 3. Dr. Steinman added that "the fever and inconsolable crying were also evidence of the

[25] In contrast, the Secretary asserted the undersigned committed a "harmless error" in revising a different finding of fact regarding when Trystan began to manifest a loss of skills. Resp't's Resp. to Mot. for Rev. at 5 n.7.

[26] The heading to this section appears to contain a typographical error in that the heading refers to Trystan's behavior on April 15-16, 2009, when the correct dates are February 15-16, 2009.

onset of neurodegeneration along with Trystan's arm contortions on February 16, 2009." Id.

Dr. Raymond differed. Dr. Raymond opined that Trystan's "discomfort and irritability are consistent with a fever associated with a viral illness." Exhibit P at 2. Dr. Raymond then directly addressed the arm contortions: "In terms of the concerns that his arms were contorting, and he was jerking around, this is consistent with an uncomfortable ill child who is tired and does not want to be held." Id. Dr. Raymond further reasoned that "[i]f arm 'contortions' were the onset of dystonia and Leigh syndrome due to basal ganglia injury, they would not be transient and subside rapidly. They would be present when he saw the provider Mr. Luna on February 17, 2009." Id. In response, Dr. Steinman re-asserted that arm contortions are not a manifestation of the common cold and emphasized the intermittent and progressive nature of dystonia across stages, citing information from the National Institutes of Health. Exhibit 196 at 2.

During the remand hearing, the Secretary raised a new point. In cross-examining Dr. Steinman, the Secretary elicited testimony that six-month-old children lack the neurological development to move their arms behind their backs voluntarily. Tr. 2054. Specifically, the process of myelination begins in the brain and progresses down the body. This progress explains why infants cannot walk until approximately 12 months old. Six-month-old children can typically pass a toy from hand-to-hand in front of their body. They may also be able to prop themselves if tipped from a seated position sideways. However, six-month-old children cannot catch themselves when tipped from a seated position backwards. Tr. 2120-24 (Dr. Raymond's testimony).

While the undersigned closed the evidentiary record after the testimony, see order issued July 10, 2020, the Sanchezes submitted new exhibits after the hearing, claiming that Dr. Raymond's "testimony was new and unexpected." Pet'rs' Remand Br. at 20. After a status conference held the day after the parties filed their briefs, the Secretary decided not to challenge the admissibility of these newly submitted articles. Resp't's Status Rep., filed July 31, 2020. Thus, exhibits 202-206 are part of the record and the undersigned has considered them.

The Secretary's position concerning the significance of the evidence regarding myelination in six-month-old children is somewhat contradictory. Initially, the Secretary commented that this evidence "is consistent with the Special Master's original fact finding that Trystan's arm contortions began when he was about a year old. 2013 Fact Ruling at 14." Resp't's Remand Br. at 14. This

statement seemed to urge the undersigned to revise the fact-finding with respect to existence or non-existence of arm contortions on February 16, 2009, again. However, in reply, the Secretary "does not contest the Special Master's finding that Trystan's 'arms contorted' on February 16, 2009." Resp't's Reply on Remand at 2.

Thus, it appears that there is no dispute that Trystan contorted his arms on February 16, 2009. See Pet'rs' Reply on Remand at 9-10. Given this finding, the ensuing question is what is the significance, if any, of the arm contortions?

b) Scope of Remand

Before discussing the significance of arm contortions, the undersigned must address the scope of the Federal Circuit's remand. The Sanchezes may be arguing that the Federal Circuit did not authorize a hearing on remand regarding the significance of the arm contortions. Pet'rs' Reply on Remand at 9.[27]

To the extent that the Sanchezes are arguing that the undersigned could not receive evidence about the significance of arm contortions on remand, this argument is not persuasive. With respect to the meaning of the arm contortions, the Sanchezes' case is analogous to E-Pass Techs., Inc. v. 3Com Corp., 473 F.3d 1213 (Fed. Cir. 2007), a case alleging infringement of a patent.

In E-Pass, the district court construed a term that appeared in the patent "electronic multi-function card." Based upon this claim construction, the district court granted 3Com's motion for summary judgment that its product did not infringe the patent both literally and under the doctrine of equivalents. However, on E-Pass's appeal, the Federal Circuit corrected the claim construction and remanded to the district court. E-Pass, 473 F.3d at 1216 (reciting procedural history). On remand, the district court granted summary judgment again, ruling that "even under a broader construction of 'card,' none of the accused devices could infringe the 'electronic multi-function card' limitation." Id. at 1217.

On the second appeal, E-Pass argued that the district court's grant of summary judgment was inconsistent with the Federal Circuit's opinion that

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[27] The Sanchezes' remand brief is ambiguous in that the Sanchezes might be arguing that the Federal Circuit did not allow reconsideration of the finding that Trystan's arm contorted. But, the remand brief could also be interpreted as arguing that the Federal Circuit did not allow evidentiary development of the finding that the arm contortions were consistent with a cold.

"'issues of material fact remain in dispute as to both literal and doctrine of equivalents infringement under the proper construction' of the term 'card.'" Id. at 1218 (quoting the previous Federal Circuit opinion, E-Pass Techs., Inc. v. 3Com Corp., 343 F.3d 1364, 1365 (Fed. Cir. 2003)). However, the Federal Circuit rejected this argument. The Federal Circuit reasoned that it "could not have intended to foreclose a summary judgment of noninfringement because the record did not yet contain the evidence that the parties would put forward in support of their infringement and noninfringement contentions under the proper construction." Id.

Thus, E-Pass teaches that when the Federal Circuit corrects an error of the trial court, the parties may develop evidence before the trial court based upon the corrected record. In E-Pass, the correction concerned claim construction. In the present case, the change concerned the existence of arm contortions. Unlike in Suel v. Sec'y of Health & Human Services, 192 F.3d 981 (Fed. Cir. 1999), cited in the Sanchezes' reply on remand, the appellate court in E-Pass remanded based on a correction to a determination made by the lower court judge that underlay the ultimate decision. The Federal Circuit in E-Pass thus did not order relitigation of a critical fact, as prohibited by the law of the case doctrine emphasized in Suel, but instead remanded for reconsideration of the ultimate decision in light of the correction. Similarly, here, the Federal Circuit identified a discrepancy in the undersigned's conclusions regarding the existence of arm contortions between findings of fact and the ultimate entitlement decision, and remanded for reconsideration in light of the arm contortion evidence based on this discrepancy. The Federal Circuit's directions for remand dictate that the evidence of arm contortions be properly considered as part of the causation analysis. Accordingly, the undersigned may consider on remand how the arm contortions affect the Sanchezes' claim that the February 5, 2009 DTaP vaccination harmed Trystan.

c) Trystan's Behaviors and Health on February 16-17, 2009

Trystan's arm contortions were just one aspect of his behavior the evening of February 16, 2009. On Ms. Sanchez's birthday, February 15, 2009, Trystan had run a fever again and was congested. Tr. 70-71. During this time, Ms. Sanchez was pregnant with her third child and suffering from nausea and headaches. Id. at 181. On February 16, 2009, the night after Ms. Sanchez's birthday, Trystan's fever became worse and, around midnight, Mr. Sanchez took a "really loud, high-pitched" crying Trystan downstairs so that his wife could get sleep. Id. at 71-72, 183. After Mr. Sanchez was able to calm Trystan, he would startle awake like he

could not breathe through his stuffy nose. Id. at 183-84. One of those times, it took Mr. Sanchez a bit longer to calm Trystan down and "he kept kicking his feet and jerking around" in Mr. Sanchez's arms, "almost as if he didn't want to be held." Id. at 184; see also Ruling Finding Facts ¶ 8.

Mr. Sanchez took Trystan back upstairs around one or two o'clock in the morning to tell his wife about Trystan's apparent discomfort. Tr. 186. Trystan's temperature was 103.2 degrees. Tr. 72, 113. The Sanchezes did not take Trystan to urgent care during the night, because after they gave him some more fever reducer and another cool bath, he fell asleep. Id. at 73-74, 187-88; see also Ruling Finding Facts ¶ 9.

On the morning of February 17, 2009, Trystan returned to the pediatrician for an urgent care visit during which he was examined and treated by Physician Assistant Jonathan P. Luna. Mr. Luna diagnosed Trystan with a "[c]ommon cold" and "[v]iral syndrome." Exhibit 1 at 48. Trystan's temperature was 98.9 degrees and "fever" was noted. Id. at 49. Ms. Sanchez told Mr. Luna that Trystan had been coughing and congested with fever. Id. at 49. The records do not indicate that Ms. Sanchez told Mr. Luna anything about Trystan exhibiting unusual arm movements or other signs of a neurological condition. See id. at 48-49; see also Ruling Finding Facts ¶ 10.

From these findings of fact, the experts analyze the various symptoms, including Trystan's high-pitched cry, fever, congestion, startling awake, jerking around, and arm contortions, and draw different inferences from them. Dr. Steinman opined, first, that Trystan had a seizure and, later, that Trystan experienced dystonia. Both Dr. Steinman and Dr. Niyazov contend that Trystan demonstrated an episode of neurodegeneration. Tr. 257, 289-90, 516, cited in Pet'rs' Remand Br. at 25. In contrast, in the December 2017 hearing, Dr. Raymond maintained that these conditions (except for the arm contortions) reflected a common cold. Tr. 830-31, 863-64.

There seems to be little reason to doubt that Trystan suffered from a common cold or some type of upper respiratory infection. Babies often suffer from colds during the winter and Trystan had older school-aged siblings who could have transmitted a virus. Tr. 359, 732. Mr. Luna, the physician's assistant who examined Trystan, diagnosed him as suffering from congestion and a common cold. Exhibit 1 at 48; see also Tr. 731-33 (Dr. McGeady's testimony about Mr. Luna's diagnosis for Trystan). While Dr. Steinman and Dr. Niyazov, at times, seemed to question the accuracy of the diagnosis of a common cold, see Tr. 413,

455; but see Tr. 2037, 2066, 2119, this skepticism over such a basic point tended to reduce the credibility of Dr. Steinman and Dr. Niyazov. By all accounts, Trystan recovered from the cold. Tr. 2042, 2066.

Trystan's February 16, 2009 fever, in turn, derives from the infection. Tr. 772-74; see also Tr. 290 (Dr. Steinman: "a cold can cause fever"). Trystan's February 16, 2009 fever differs from the February 5, 2009 fever, which ebbed and flowed for a "few days." Ruling Finding Facts ¶ 7; see also id. ¶ 8 (On February 15, 2009, "Trystan had run a fever *again*") (emphasis added). As Dr. McGeady correctly interpreted the Ruling Finding Facts, Trystan's February 5, 2009 fever did not last through February 15, 2009. Tr. 731 (Dr. McGeady), 830 (Dr. Raymond). Dr. Niyazov's suggestion that Trystan suffered a continuous fever is not in accord with the Ruling Finding Facts. See Tr. 455, 495. Even so, Dr. Niyazov could not say that the February 5, 2009 vaccination caused the February 15, 2009 fever. Tr. 502.

Beyond the fever and congestion that are part of a common cold, Trystan also cried, startled awake, jerked around in his father's arms, and, most importantly for this remand decision, contorted his arms. These behaviors are the foundations for Dr. Steinman's opinion that Trystan suffered a seizure or dystonia.

The changes in the inferences that Dr. Steinman drew from these behaviors tend to diminish Dr. Steinman's credibility. To review, Mr. Sanchez averred that Trystan's arms contorted on February 16, 2009. Exhibit 4 ¶ 6. Based upon Mr. Sanchez's affidavit, Dr. Steinman's first report stated that Trystan "may have had a seizure" and "suffered from seizures." Exhibit 2 (Dr. Steinman's Sept. 28, 2011 report) at 1-2.

As revealed during the December 2017 hearing, the confidence with which Dr. Steinman opined that Trystan suffered a seizure based upon Mr. Sanchez's affidavit was overstated. Dr. Steinman recognized that only an electroencephalogram (EEG) would allow a diagnosis of a seizure. Dr. Steinman testified:

> Kicking feet and jerking around. Is that evidence of a seizure? Is it evidence of rebelliousness or discomfort? I don't know. In any particular feature like that that you hear about in a history or observe, unless you had a video EEG with a set event, kicking feet and jerking around, coupled to an electroencephalogram, you couldn't say for sure is that a

> seizure, but kicking feet and jerking around could be an encephalopathy.

Tr. 257. Later, Dr. Steinman elaborated on the usefulness of an EEG:

> [I]f something is in doubt, if there's a stiff arm or an abnormal movement, we can hook an EEG up to a free-moving person and see what's happening, but in the absence of that, what is making a lot of speculation on what is a seizure, what is a non-seizure. And I can't answer on any piece of history in the literature that came from a parent or a nurse practitioner or a doctor recording a history, what exactly was a seizure and what exactly wasn't a seizure.

Tr. 284-85. Dr. Steinman also described how even experts in epilepsy have difficulty determining a seizure in the absence of an EEG. Dr. Steinman stated: "I go to EEG report when I'm on duty and I see that happening by people who think about epilepsy all day long and their blinded taste test, so to speak, without the EEG shows we're not very good at guessing." Tr. 285. Dr. Steinman's first report in which he stated Trystan "may" have had a seizure and Trystan "suffered" seizures did not disclose any limitations on the ability of a neurologist to identify a seizure. Nevertheless, Dr. Steinman's "educated opinion is that the seizure began eleven days after the vaccination." Tr. 288; accord Tr. 357.

After the weakness in his opinion regarding Trystan's February 16, 2009 behavior as a seizure was brought out, Dr. Steinman shifted to say that a finding that Trystan suffered a seizure was not necessary to his opinion. Tr. 292, 358. In this context, Dr. Steinman offered the opinion that Trystan's arm contortions were dystonic posturing. Tr. 358. Given that the only source of information about Trystan's arm contortions on February 16, 2009, was Mr. Sanchez and this information was equally available to Dr. Steinman when Dr. Steinman wrote his *first* report, Dr. Steinman's belated conclusion that the February 16, 2009 activities were dystonic is surprising.[28]

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[28] The Secretary takes Dr. Steinman to task for failing to identify Trystan's arm contortions in his first *five* reports. Resp't's Remand Br. at 15-16. However, this criticism goes too far because Dr. Steinman wrote *four* of those reports after the Ruling Finding Facts (temporally) removed the arm contortions as a fact on which the experts could base their

Regardless of when Dr. Steinman came to the opinion that Trystan had dystonia on February 16, 2009, Dr. Steinman's current opinion is that Trystan had dystonia and a seizure. See exhibit 196 at 3.[29] Dr. Steinman's opinion that Trystan suffered a seizure on February 16, 2009, is not persuasive.

First, as discussed above, Dr. Steinman undercuts the ability of any neurologist, even epileptologists, to identify a seizure without an EEG. In Dr. Steinman's words, "the batting average of their predictions isn't that great." Tr. 285.

Second, when Trystan eventually developed seizures, Trystan's seizures involved deviation of his head and eye, an altered consciousness, and a postictal period. Exhibit 138 at 99 (Dr. Wong's Dec. 7, 2010 report); see also exhibit P (Dr. Raymond's June 19, 2020 report) at 3 (citing this medical record), Resp't's Remand Br. at 16 (citing Dr. Raymond's report). This presentation seems too different from the arm contortions on February 16, 2009, and too long after to find a pattern of seizures.

Third, Dr. Raymond disagreed with Dr. Steinman. Exhibit P at 3. Dr. Raymond wrote this report after remand for consideration of the arm contortions. Thus, while Dr. Raymond's testimony in the December 2017 hearing did not account for arm contortions, see Tr. 830, his more recent opinion is based upon all the facts.

Finally, at an August 7, 2012 appointment, one of Trystan's treating physicians, Dr. Haas, noted that Ms. Sanchez reported arm contortions following the February 5, 2009 vaccination. Exhibit 26 at 1. However, while Dr. Haas noted these arm contortions, this appointment occurred three years after the vaccination, and Dr. Haas did not assess the arm contortions as indicative of a seizure or neurological issues. Id. at 3. The most Dr. Haas did was to memorialize Mr.

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opinions. See Pet'rs' Remand Br. at 24. On the other hand, the Sanchezes are too quick to exonerate Dr. Steinman because they overlook his *first* report.

[29] After the hearing, the Sanchezes introduced exhibits 202-05 to demonstrate that a seizure can lead to dystonic posturing. The Sanchezes asserted that these articles were in response to a question about the consistency of Dr. Steinman's opinions. Pet'rs' Remand Br. at 26. However, given that Dr. Steinman had already disclosed an opinion that Trystan suffered both a seizure and dystonia on February 16, 2009 (exhibit 197), the Sanchezes appear to have been capable of filing the exhibits in advance of the hearing.

Sanchez's report that Trystan's cousin "also had a dystonic reaction" to her one-year-old vaccinations. Id. at 1.

For these reasons, the undersigned finds that the Sanchezes have not established with preponderant evidence that Trystan suffered a seizure on February 16, 2009. With the elimination of a seizure, the next issue is whether Trystan suffered dystonia.

Dystonia is "dyskinetic movements due to disordered tonicity of muscle." Dorland's Illustrated Medical Dictionary 576 (32d ed. 2012). "Dyskinesia," the root for the term "dyskinetic" in that definition, means "distortion or impairment of voluntary movement, as in tic, spasm, or myoclonus." Id. at 572. Dr. Steinman elaborated that dystonia is a neurologic problem ultimately manifesting in a problem in posture. Tr. 2025. The source of dystonia is a problem in a part of the brain known as the basal ganglia. Tr. 2025, 2157.[30] Dystonia can be a manifestation of many neurologic disorders. Tr. 2026.

Dystonia can be a manifestation of Leigh's syndrome. In one study of Leigh's syndrome, researchers investigated the background of 130 patients with Leigh's syndrome. After excluding patients with abnormal motor findings of unknown onset, the group consisted of 57 patients. Of this group, 15 (or 26 percent) had dystonia at the onset of their Leigh's syndrome with another 42 (or 74 percent of the 57 patients) developing dystonia later. Court exhibit 1003; accord Tr. 2155-56 (Dr. Raymond acknowledging that although dystonia often starts later in Leigh's syndrome, dystonia can start earlier too).[31] As Dr. Steinman noted "even though dystonia may be less frequent at onset, [dystonia] is still listed." Exhibit 185 at 2; accord Tr. 2157. The cumulative probability of having an onset of Leigh's syndrome with dystonia at six months is approximately five percent. Kalliopi Sofou et al., *A multicenter study on Leigh syndrome: disease course and*

[30] An MRI performed in December 2009 revealed that Trystan had a problem in his basal ganglia. Exhibit 1 at 142, 130.

[31] This Court exhibit comes from an article (Sofou) that Dr. Steinman cited. Exhibit 95 (Dr. Steinman's Dec. 10, 2015 report) at 17-19; exhibit 185 (Dr. Steinman's June 15, 2020 report) at 2-3. The Sanchezes filed Sofou as the article was published in written form as exhibit 97. The version of the Sofou article available on-line contains "additional files." See exhibit 97 at 15. Of those additional files, the Court exhibit contains a relevant additional file, Table S2.

predictors of survival, 9 Orphanet J. Rare Diseases, at pdf 6, figure 3 (2014), filed as exhibit 97; see also Tr. 2117-18.

In Dr. Raymond's view, the progression of myelination affects the areas in which dystonia can appear. Dystonia "typically is in those motor patterns that [infants] have myelinated." Tr. 2118. Dr. Raymond explained that a condition called paroxysmal infant dystonia occurs in children a couple months to seven or eight months old in which infants have abnormal "hand movements in front of them." Tr. 2118.

Dr. Steinman and Dr. Raymond disputed the degree to which myelination permits or prevents six-month-old infants from manifesting dystonia by moving their arms behind their backs. Although Dr. Steinman recognized that six-month-old infants lack the ability to prevent themselves from falling backward when pushed from a seated position, Dr. Steinman pointed out that myelination is a developmental process. In his view, the myelination process "doesn't mean that there's not enough myelin to transmit abnormal nerve impulses leading to dystonia." Tr. 2157-58. In contrast, Dr. Raymond stated that he "disagree[s] that you can have that type of movement without appropriate myelination. So that when we look at infantile dystonias, we are typically looking at – no, not typically, we are always looking at movements that are following their usual repertoire in that the basal ganglia is affecting that with an abnormality." Tr. 2176-77.[32]

As an abstract question whether six-month-old infants are sufficiently myelinated to experience dystonia by moving their arms backward is difficult to answer on this case's evidentiary record.[33] Dr. Steinman and Dr. Raymond are both neurologists with decades of experience. Each has some experience with pediatrics—Dr. Steinman holds a chair for pediatrics and Dr. Raymond held a board certification in pediatrics from 1991-2005.[34] Thus, each is qualified to offer opinions. If the undersigned were forced to credit the opinion of one qualified

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[32] The transcript at 2176:13 and 2176:21 misidentified the speaker as Ms. Reynaud, the attorney for the Secretary. The context indicates that Dr. Raymond spoke.

[33] After the hearing, the Sanchezes submitted an article concerning the myelination of the brain. Exhibit 206. However, this article does not help in determining the extent of myelination in the peripheral nervous system, including the nerves that control the muscles for backward arm movement.

[34] However, as noted earlier in this decision, the Sanchezes did not seek to have Dr. Steinman admitted as an expert in pediatrics.

expert and to reject the opinion of another qualified expert strictly based on qualifications, the undersigned would be inclined to find Dr. Raymond more qualified on this narrow point. Early in his career (1989-90), Dr. Raymond was a fellow in "developmental neuropathology." Exhibit M (curriculum vitae) at 1. Dr. Steinman's fellowship was in chemical immunology. Exhibit 168 (curriculum vitae) at 1. This difference in advanced specialization would break any tie in Dr. Raymond's favor.

On the more specific question as to whether Trystan experienced dystonia on February 16, 2009, the evidence is firmer that he did not. Both experts agree that dystonia originates in the basal ganglia. Tr. 2025, 2157. Before the hearing Dr. Raymond had written: "If Trystan were having arm contortions in February 2009 due to Leigh syndrome and basal ganglia injury, they would have been persistent and obvious and it is expected that his attentive parents would have brought it to the attention of his providers as they did for his other illnesses." Exhibit P at 2-3. Dr. Raymond's testimony was similar. He maintained that "[i]f we look at basal ganglia injury for whatever reason, it typically – it typically presents initially with hypotonia, and it only much later presents with dystonia." Tr. 2177. Although given an opportunity to address this sequence, the Sanchezes did not present any contrary testimony. Tr. 2177.

Further, it seems unlikely that Trystan would experience an episode of dystonia that is caused by an injury in his basal ganglia one time in February 2009 and not experience any other motor problems for months. Cf. O'Connell v. Sec'y of Health & Human Servs., No. 96-63V, 1998 WL 64185, at *12 (Fed. Cl. Spec. Mstr. Feb. 2, 1998) (deeming "arm jerking" immediately post-vaccination as not indicating the onset of neurological issues in part because of the lack of medical attention and follow-up, even where seizure activity developed weeks later), mot. for rev. denied, 40 Fed. Cl. 891 (1998), aff'd in unpublished op., 217 F.3d 857 (Fed. Cir. 1999); Lara v. Sec'y of Health & Human Servs., No. 90-1655V, 1993 WL 215068 (Fed. Cl. June 4, 1993) (a child having eye fluttering five to six times per days several days a week as well as "whole body jerks" from age two-months to four-months was found to have seizures before receiving a vaccination at age four-months). While Dr. Steinman states that "the dynamic effect of the shot was to create damage in the nervous system," Tr. 295, and that dystonia can be "intermittent," see exhibit 196 (Dr. Steinman's June 22, 2020 report) at 2; Tr. 2029, Dr. Steinman could not specify how frequently even "intermittent" dystonia appears. Tr. 2029. Dr. Steinman's opinion suggesting that Trystan could have dystonia in February but not again for many months is not persuasive.

Therefore, the undersigned finds that the Sanchezes have not shown by preponderant evidence that Trystan's February 16, 2009 arm contortions were a manifestation of a seizure or an episode of dystonia. For the reasons explained above, the February 16, 2009 arm contortions do not constitute a neurologic abnormality caused by his vaccination. Because the Sanchezes bear the burden to establish the onset of Trystan's neurologic injury caused by the vaccination and because they have not met this burden, the analysis of the arm contortions can end here.

If more about the arm contortions is needed, then Dr. Raymond's opinion is credible. Dr. Raymond stated, "In terms of the concerns that his arms were contorting, and he was jerking around, this is consistent with an uncomfortable ill child who is tired and does not want to be held." Exhibit P at 2. Dr. Raymond's post-remand supplemental opinion, which includes arm contortion, is in accord with his December 2017 testimony. Tr. 863, 874.

Dr. Steinman stated that "'arm contortions,' known as dystonic posturing, are not associated with the common cold." Exhibit 185 at 2; see also Tr. 460-61, 462-63, 516 (Dr. Niyazov testifying that Trystan's arm contortions likely constituted neurodegenerative events). However, the undersigned has found that Trystan's February 16, 2009 arm contortions are not a manifestation of dystonic posturing. Although arm contortions could be a neurologic finding, Tr. 2142, they do not have to be. For Trystan, in February 2009, the arm contortions were not a manifestation of a neurologic injury.

3. End of February to beginning of April 2009

The next period of Trystan's life, from the resolution of his cold near the end of February through the beginning of April 2009, strongly influences the outcome of the Sanchezes' claim for compensation. As noted above, the Sanchezes argue that the vaccination altered Trystan's development. In the words of their primary expert, Dr. Steinman, in February 2009, Trystan took a "big hit." Tr. 2042. However, as reviewed in this section, evidence of this alleged "big hit" does not appear in the ensuing weeks.

Between the February 17, 2009 appointment with Mr. Luna and the April 29, 2009 appointment with Dr. Seleem, Trystan did not see any medical providers. As detailed in paragraphs 12-13 of the Ruling Finding Facts,

> 12. Sometime [after February 17, 2009], Trystan's extended family gathered to watch a boxing match. Tr. at 25, 219.

> During this gathering, Trystan was sick, crying, fussy, and congested. Id. at 191. He was not contorting his arms nor was he limp or rigid.
>
> 13. Between [Ms. Sanchez]'s birthday and the next time she took him to the doctor nearly two months later in late April, Trystan suffered from cough and congestion episodically. Exhibit 1 at 50. During this time, he did not lose control of his head and trunk, nor did he stop making eye contact or stop wanting to play anymore. He did not exhibit arm contortions.

Ruling Finding Facts at 13, ¶¶ 12-13. The October 9, 2018 decision similarly stated that "[b]etween the February 17, 2009 visit with Mr. Luna and the April 29, 2009 visit with Dr. Seleem, Trystan did not have any symptoms that were inconsistent with a cold." Decision at 8, 2018 WL 5856556, at *4. These facts are not contested.[35]

Neither Dr. Steinman nor Dr. Niyazov can identify any behavior in Trystan that shows evidence of neurodegeneration or neurologic problem between the February 16, 2009 cold and Trystan's loss of skills. Dr. Niyazov was asked about evidence that Trystan had neurodegenerative events between February 5th and June 1st. Dr. Niyazov responded: "Inconsolable crying, loud high-pitched crying, kicking feet and jerking around, contorting arms, and then no walking, standing -- well that's six months." Tr. 516. Significantly, Dr. Niyazov has identified behaviors that happened on February 16, 2009: "Inconsolable crying, loud high-pitched crying, kicking feet and jerking around, contorting arms." He did not identify another behavior in the relevant time as Trystan would not be expected to walk until around his first birthday. Ms. Marin-Tucker noted a delay in Trystan's ability to walk; however, this was at Trystan's May 2009 appointment, months later. Exhibit 1 at 54 ("[can] not walk or stand, extremities seem soft yet rigid at times, rolls a little, head lag, no crawling").

In lieu of any factual findings that Trystan displayed any abnormal behaviors, Dr. Steinman and Dr. Niyazov attempt to excuse the lack of findings. To some extent, as the October 9, 2018 decision recognized, parents may not

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[35] In their motion for review, the Sanchezes argued that the submission of Ms. Sanchez's day planner should have altered the findings of fact. Pet'rs' Mot. for Rev. at 3. However, the Court of Federal Claims rejected that argument. Opinion and Order at 250-51. The Sanchezes did not further pursue this argument to the Federal Circuit.

notice that their child is failing to meet milestones or conceivably, parents may not notice that their child is losing skills he once had. Decision at 27, 2018 WL 5856556, at *16; see also Tr. 313 (Dr. Steinman commenting on observations). However, according to Dr. Raymond, a child with damaged basal ganglia is likely to have low tone and maybe abnormalities in eye movement or breathing issues. Tr. 2127. However, there is no persuasive evidence of abnormal eye movements or hypotonia from the end of February for many weeks.

Alternatively, the Sanchezes maintain that Trystan experienced a "fade" response as described in the Naviaux commentary to the Shoffner article. See Pet'rs' Remand Br. at 51-53. For this argument, the Sanchezes primarily rely upon Dr. Niyazov's testimony, although Dr. Steinman similarly suggested that the progression of Trystan's condition might stop and stutter. Tr. 298.

Preliminarily, the value of the Naviaux commentary is uncertain. The account that Dr. Niyazov presented came from a blog of the website for the group Autism Speaks. See exhibit 68 (Dr. Niyazov's report) at 13 (bibliography); Bob Naviaux, Commentary on *Fever Plus Mitochondrial Disease Could Be Risk Factors for Autistic Regression by Shoffner et al.*, filed as exhibit 80. Dr. Niyazov did not know whether the Naviaux commentary was peer-reviewed. Tr. 526. While the lack of peer review could diminish the value of opinions expressed, Dr. Niyazov vouched for Dr. Naviaux's credentials, describing Dr. Naviaux as a "very trusted and respected person, an expert in the field of mitochondrial disease." Tr. 526. A second issue is that the underlying Shoffner article and Naviaux commentary are written about children with autism, which is not Trystan's disease. See Tr. 310, 833-34; see also H.L. v. Sec'y of Health & Human Servs., No. 10-0197V, 2016 WL 3751848, at *17 (Fed. Cl. Spec. Mstr. Mar. 17, 2016) (petitioner's witness "admitted that she is not aware of any reliable study attributing acute metabolic decompensation to a flu vaccine among patients with Leigh Disease"), mot. for rev. denied, 129 Fed. Cl. 165 (2016), aff'd, 715 F. App'x 990 (Fed. Cir. 2017). But, this issue, too, can be set aside to address the substance of the argument that Trystan faded.

Dr. Naviaux stated "[w]hen children with the common forms of mitochondrial disease suffer a regression, it is most often a 'fade' response. The fade response is typically delayed for 2-10 days after a fever resolves." Exhibit 80 (Naviaux) at 2 (underline in original). Based upon reports from parents, Dr. Naviaux describes the fade response: "the child was getting better from their cold or flu, when suddenly, their consciousness fades. The child can become difficult to fully awaken, or will stop walking, stop talking, stiffen or lose muscle tone, or have a seizure, or a stroke-like episode." Id. The Sanchezes state in multiple

places that Trystan suffered a fade response. See, e.g., Pet'rs' Remand Br. at 37, 52. The Sanchezes rightfully point out that Trystan had not yet developed the ability to walk or to talk.

However, there is not preponderant evidence that Trystan experienced a fade as Dr. Naviaux has described. There is no evidence that in the months after his February 5, 2009 vaccination, Trystan began to lose consciousness or was difficult to awaken. In contrast, the Ruling Finding Facts found that Trystan continued to play. Similarly, there appears to be no evidence that between February 17, 2009, and at least May 1, 2009, that Trystan suffered a seizure or stroke-like episode. Trystan did have arm contortions on February 16, 2009. But, that episode was short-lived, singular, and did not signify a neurologic injury due to vaccination. The Ruling Finding Facts found that during a boxing match the family watched after February 17, 2009, Trystan was neither limp nor rigid. Therefore, the argument that Trystan is like the children reported in the Naviaux commentary advanced by Dr. Niyazov is inapt.

So, too, are comparisons between Trystan and Karl Paluck. By way of review, approximately 2-3 weeks after vaccination, Karl experienced such worsened stiffness in his limbs that his parents took him to a chiropractor for several visits. Paluck v. Sec'y of Health & Human Servs., 786 F.3d 1373, 1376 (Fed. Cir. 2015). In the ensuing months, Karl's pediatric neurologist noted that Karl suffered from "gross motor delay, global developmental delay, and hypertonicity." Id. A later MRI confirmed a thinning of the corporal collosum. Id. Karl suffered seizures and was later diagnosed with an unspecified mitochondrial disorder. Id. Trystan did not manifest a progression of stiffness in his limbs for which his parents sought medical attention.

While the Sanchezes have also compared Trystan to Hannah Poling, that analogy does not hold true. Dr. Naviaux pointed to Hannah Poling as an example of the "flare" response. As weak as the evidence that Trystan suffered a fade is, any claim that Trystan suffered a flare is even weaker. Dr. Naviaux describes a flare as "occur[ing] early, at the peak of the fever and inflammatory response, within 2-3 days of infection. During a flare response, there is a high fever, often over 102°F, and hyperirritability, crying, inconsolability, a disrupted sleep-wake cycle, and a refusal to walk in children who might otherwise appear physically able to walk." Exhibit 80 (Naviaux) at 2 (underline in original). "Following a flare response, there can be a gradual evolution of other problems from persistent GI problems and diarrhea, a gradual loss of language over 2-3 months, with the onset of repetitive movements, to gaze avoidance and social avoidance. It must be emphasized that a flare response is not simply a high fever, or even a dramatic

reaction to a high fever, like a febrile seizure." Id. Except for inconsolable crying and fever, Trystan did not have problems such as a disrupted sleep-wake cycle, gastrointestinal problems, or social avoidance.

In sum, Trystan did not present like any of the children to whom the Sanchezes have compared him.[36] The undersigned recognizes that Trystan does not have to match any of these prior cases. On the other hand, the prior cases do start to form a tentative pattern in which children who may have been harmed by a vaccination show evidence of decline within a few weeks of the vaccination. The evidence of decline might "ebb and flow." Tr. 460. But, even a progression that ebbs and flows has some periods in which the child displays some worsening symptoms. Here, Trystan did not.

Implications for Althen Prong 3

As discussed earlier, Althen prong 3 requires (a) persuasive evidence about the timeframe between a vaccination and the onset of a problem for which inferring causation is appropriate and (b) persuasive evidence that the onset occurred in that time. The undersigned has found that the evidence tends to suggest that the expected interval is around two weeks, although this period cannot be rigidly defined.

Within two weeks, Trystan did experience two episodes. First, on the day and night of vaccination, he experienced a fever, inconsolable crying, and a mark on his leg. Second, approximately 11 days later, Trystan had a common cold. In association with this cold, Trystan experienced a fever, congestion, restlessness, jerking around, and arm contortions. Taken in isolation, each seems to be a relatively benign, if not typical, part of infancy.

However, as Dr. Steinman stated, context matters. Tr. 257, 265, 325, 2019, 2057. If, in the following weeks and months, Trystan had displayed neurologic problems, such as spasticity for which his parents sought treatment like Karl Paluck or the consistent eye blinking of Ashlyn Markovich, then the relatively benign episodes could be viewed in context as more significant. But, Trystan did not display any behaviors that suggested any neurologic problems from February 17, 2009, to at least May 1, 2009, well beyond the approximate two-week onset of

[36] In the context of genetics, Dr. Niyazov accused Dr. Raymond of "cherry-picking" cases that support Dr. Raymond's opinion. Tr. 2162. But, the comparisons offered in the text are comparisons from cases and articles that the Sanchezes have offered.

symptoms anticipated by the Sanchezes' medical theory. Consequently, the Sanchezes have failed to meet their burden of proof regarding prong 3.[37]

4. April to May 2009

As previously described, from the end of February through approximately mid-April, Trystan experienced relatively good health. He did have episodes of coughing and congestion occasionally. Ruling Findings Fact, issued April 10, 2013, ¶ 13.

> On April 29, 2009, when pediatrician Dr. Nabil R. Seleem saw Trystan, then eight and a half months old, he noted that Trystan had suffered cough and congestion for two weeks. No unusual arm movements or developmental issues were reported. In his neurological review, Dr. Seleem noted "[n]o neurological symptoms." Ultimately, he diagnosed Trystan with an ear infection and bronchitis and prescribed amoxicillin. Exhibit 1 at 50-52.

Ruling Finding Facts ¶ 14. Additionally,

> Dr. Seleem did not observe any signs consistent with a neurological injury during the examination performed on Trystan during the April 29, 2009 visit. Instead, Trystan had a cold.

Decision at 8, 2018 WL 5856556, at *4.

> Trystan's mother and grandmother brought Trystan back to the clinic to see Dr. Brown on May 13, 2009. Dr. Brown observed that Trystan's infection appeared to be resolving, and recommended continued use of a humidifier. No reports of the loss of eye contact or an inability to roll over were made at this time. Exhibit 1 at 53.

Ruling Finding Facts ¶ 15.

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[37] To be clear, in determining that the Sanchezes have not met their burden regarding prong 3, the undersigned has not considered the effect of the colds for which Trystan was treated on April 29, 2009, and May 13, 2009.

As noted in the October 9, 2018 decision, Dr. Steinman and Dr. Niyazov largely ignored the visits with Dr. Seleem and Dr. Brown. This oversight is most readily apparent in demonstrative exhibits used during Dr. Steinman's and Dr. Niyazov's testimony. See exhibits 162 and 165; see also Tr. 338-39 (Dr. Steinman's testimony in reference to exhibit 162), 458-59 (Dr. Niyazov's testimony in reference to his timeline). Both demonstrative exhibits omit a summary of these visits on their timelines.

Other examples of Dr. Steinman and Dr. Niyazov skipping over the visits for colds appear as well. Dr. Niyazov testified: "We can only follow February 5th and 16th and August 8th and June 1st." Tr. 462. This list does not include observations from Dr. Seleem and Dr. Brown.

In the hearing on remand, when asked for the next data point along Trystan's "downward cascade" following the February 16-17, 2009 episode, Dr. Steinman pointed to the second set of vaccinations, which occurred in August 2009. Tr. 2035-36. Similarly, early in Dr. Steinman's testimony during December 2017, he described Trystan as a "healthy well child and following that February 5th immunization and then even more dramatically after the August -- mid August 2nd encounter that we call response, he had neurologic deterioration." Tr. 292. Similarly, Dr. Steinman stated: "there's no doubt it began February 5th, it worsened in mid August." Tr. 293.

A question from the Sanchezes' attorney also shows how Dr. Steinman minimized the illnesses:

> Q: If Trystan had a couple colds between February 16 and June 1, would that impact your opinion regarding this continuous process?
>
> A: No. I mean, children in the winter are going to get respiratory infections, so it's the unusual child who would not have that.

Tr. 298. The question is posed as a hypothetical but there is no dispute that Trystan had colds in the relevant time.

Dr. Steinman's dismissal of the sicknesses is inconsistent with his later testimony that "infections . . . can devastate or kill" children with mitochondrial diseases. Tr. 312; accord Tr. 2044. Later, in response to a question from the undersigned, Dr. Steinman recognized that infections could contribute to Trystan's

Leigh's syndrome but the infections did not because Trystan did not have a fever. Tr. 360-61. Dr. Steinman repeated this opinion in the remand hearing in which he stated that "small" colds would not affect Trystan. Tr. 2043-44.

Dr. Niyazov also admitted that "if anything comes in in the meantime [referring to the period between February 16, 2009, and the loss of skills on June 1, 2009] and hits the child's system again, like a fever of 103, . . . then that will contribute to that fade response." Tr. 459; accord Tr. 2076. Dr. Niyazov did make some attempt to fit the colds into his overall theory of the case by stressing Trystan's vulnerability, as evidenced by the following exchange during the original entitlement hearing:

> Q: Now, if there were some other illnesses between February 16th and June 1st, what impact would those have on Trystan who's now more susceptible and his energy levels are ebbing and flowing, if I'm hearing that correctly?
>
> A: Right. So there will be -- it will have a detrimental effect and it will decrease the energy further and, at some point, he would start losing skills.

Tr. 460; accord Tr. 2076.

The undersigned recognizes that in Dr. Steinman's and Dr. Niyazov's view, Trystan started a decline on February 5, 2009. Thus, they could reasonably assert that the colds in April and May only contributed to an on-going process. The flaw, however, is that, for the reasons explained at length above, the Sanchezes have not presented persuasive evidence that Trystan's decline started on February 5, 2009. See Tr. 2124 (Dr. Raymond).

Instead, if Trystan did not start a neurologic decline until May 1, 2009, at the earliest—as the October 9, 2018 decision finds and this decision confirms—then the analysis proceeds differently. If it is assumed for the sake of argument that a trigger, such as an upper respiratory infection, could influence the outcome of a child with Trystan's genetic mutations, then the infection is a more likely trigger for the neurologic decline. The sequence of events fits much better. On April 29, 2009, Ms. Sanchez reported that Trystan had been ill for two weeks. Exhibit 1 at 50-52. Then, Trystan started to lose developmental skills perhaps as early as May 1, 2009, which would be approximately two weeks after he became infected. At the August 17, 2009 primary care visit, Ms. Marin-Tucker noted certain developmental delays and loss of skills that Ms. Sanchez reported began occurring

"2-3 months ago" (i.e., around May 17, 2009, or June 17, 2009). Id. at 54. This loss of skills included "[can] not walk or stand, extremities seem soft yet rigid at times, rolls a little, head lag, no crawling, . . . can [not] sit or grasp." Id. Ms. Marin-Tucker also noted "speech and language deficits" and "developmental delays." Id.

As discussed in the context of prong 3, Edmonds and Shoffner suggest that an appropriate interval to infer causation is approximately two weeks between the inciting event and the onset of decline. Edmonds and Shoffner, therefore, align with an account that Trystan's neurodegeneration began around May 1, 2009. But, to repeat, the foregoing analysis assumes that a trigger is needed. Thus, assuming this medical theory and, in light of Trystan's May 2009 onset of neurodegeneration, it is more likely that Trystan's infections between February and May 2009 caused the manifestation of his Leigh's syndrome, independent of his vaccinations.

5. August 2009

The following facts were established in the Ruling Findings Fact:

> 19. At [Ms. Sanchez]'s baby shower, on August 8, 2009, Trystan exhibited inconsolable crying. Tr. 25, 45-46, 88-89, 137, 159. At times, instead of being rigid, his body was limp, as if he had no muscle tone. Id. at 46, 53. At other times during this day, he was contorting his arm. Id. at 89, 137, 160.
>
> 20. At one year old, Trystan was seen by Physician Assistant Micaela Marin-Tucker for a well-child exam. Exhibit 1 at 54-56; Tr. 89-90. Ms. Sanchez informed Ms. Marin-Tucker that she "noticed a change in [Trystan's] development about 2-3 months ago[38] but since she had taken [Trystan to the pediatric clinic] with Dr. Brown she thought that everything was ok."[39]

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[38] According to this report, Trystan's developmental changes began between May 17, 2009, and June 17, 2009.

[39] Ms. Sanchez testified that she had reported to Ms. Marin-Tucker that Trystan's developmental changes began five to six months before his August 17, 2009 visit, which would be between February 17, 2009, and March 17, 2009. Tr. 90-91. Ms. Sanchez's August 17, 2009 recounting of the onset of Trystan's developmental delays is more reliable than testimony offered more than two years after his visit to Ms. Marin-Tucker. Testimony offered so long after

> Exhibit 1 at 54. (This history is the basis for the conclusion in paragraph 18 that Trystan's loss of skills began around June 1, 2009.) Upon a review of systems, Ms. Marin-Tucker found that Trystan did not walk, stand, crawl, and hold his head up while sitting, or make any attempt to move his lower extremities. She also noted in her examination that his extremities seemed soft, yet rigid at times. As the result of her examination, Ms. Marin-Tucker ordered a battery of lab tests. Exhibit 1 at 54-55. She also referred Trystan to a neurologist, physical therapist, and occupational therapist. Id. at 55; Tr. 90. Additionally, Trystan received his third hepatitis B vaccine, as well as his second doses of the pneumococcal conjugate, DTaP, and Hib vaccines. Exhibit 1 at 55; Tr. 92. Trystan was to return to the nurse the next week to receive the remaining vaccinations that were due, including the measles, mumps, and rubella, varicella, and hepatitis A vaccines. Exhibit 1 at 55.

Ruling Findings Facts ¶¶ 19-20.

Before considering how Trystan fared *after* his second set of vaccinations, Trystan's developmental status on the day he received his second set of vaccinations should be established. Some information about Trystan's health before the second set of vaccinations comes from his family's testimony about his behavior during the baby shower on August 9, 2009.

This testimony credibly established that Trystan lacked muscle tone and was having arm contortions. Trystan's behavior appears to fit how Dr. Raymond asserted that problems originating in the basal ganglia would present: first with hypotonia and later with dystonia. See Tr. 2177. Furthermore, a decline starting in May or June through August 17, 2009, would be consistent with Dr. Naviaux's fade response. Tr. 833 (Dr. Raymond).

Otherwise, the experts did not focus too much on Trystan's developmental status just before August 17, 2009. Dr. Steinman recognized that by the date of Ms. Marin-Tucker's examination, Trystan's loss of skills had been going on for some time. Tr. 296-97; see also Tr. 2124 (Dr. Raymond). Rather, Trystan's status

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the events in question is less reliable than reports provided closer in time, when the motivation for accurate explication of symptoms is more immediate.

on the day of his second set of vaccinations forms a foundation for the argument that Trystan experienced a rechallenge.

6. October – December 2009, including Rechallenge

Information about Trystan's development following his August 17, 2009 vaccinations is scarce. The Ruling Findings Facts stated:

> 21. About six weeks [after the August 17, 2009 vaccination], on October 7, 2009, both Jennifer and Germain went to see Ms. Marin-Tucker for a follow-up. In a review of Trystan's systems, Ms. Marin-Tucker noted no seizures, weakness, or tics. She made no notation of tremors or twitching. Upon neurologic examination, she found Trystan to be unable to grasp, sit, crawl, or make much eye contact. Germain reported that there was "another child in the family with the same symptoms and doctors [could] find nothing wrong." Ms. Marin-Tucker emphasized the importance of making the appointment with a neurologist as soon as possible. Exhibit 1 at 57-58.

Ruling Finding Facts ¶ 21. This statement also appears in the October 9, 2018 decision.

Based upon Ms. Marin-Tucker's notes from two appointments, Dr. Steinman characterized this "as a worsening of [Trystan's] neurologic condition" after his second vaccinations. Tr. 336. This conclusion is reasonable. However, the ensuing question is whether the Sanchezes have established that the challenge-rechallenge paradigm fits this case.

Evidence of challenge-rechallenge can be powerful evidence in support of a claim that a vaccine harmed an individual. See Koehn v. Sec'y of Health & Human Servs., No. 11-355V, 2013 WL 3214877, at *30 (Fed. Cl. Spec. Mstr. May 30, 2013), mot. for rev. denied, 113 Fed. Cl. 757 (2013), aff'd, 773 F.3d 1239 (Fed. Cir. 2014). "A rechallenge event occurs when a patient who had an adverse reaction to a vaccine suffers worsened symptoms after an additional injection of the vaccine." Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1322 (Fed. Cir. 2006). To this basic definition, Dr. Raymond added that "[t]he challenge should meet the criteria of same latency and same effects, and must exclude well-accepted alternative explanations." Exhibit P at 4.

The Sanchezes criticize Dr. Raymond for not adopting the "legal definition" of rechallenge. Pet'rs' Remand Br. at 38 n.15. However, to the extent that Dr. Raymond is promoting the idea that the challenge and the rechallenge events should be similar or the same, this concept has appeared in other cases from a variety of sources. See, e.g., R.V. v. Sec'y of Health & Human Servs., No. 08-504V, 2016 WL 3882519, at *19 n.62 (Fed. Cl. Spec. Mstr. Feb. 19, 2016) (relying upon Dr. Shafrir), mot. for rev. denied, 127 Fed. Cl. 136 (2016), app. dismissed, Fed. Cir. 16-2400 (Oct. 26, 2016); Tompkins v. Sec'y of Health & Human Servs., No. 10-261V, 2013 WL 3498652, at *27 n.68 (Fed. Cl. Spec. Mstr. June 21, 2013) (citing report from Institute of Medicine), mot. for rev. denied, 117 Fed. Cl. 713 (2014); Freeman v. Sec'y of Health & Human Servs., No. 04-1528V, 2009 WL 5103594, at *12 (Fed. Cl. Spec. Mstr. Dec. 9, 2009) (relying upon opinion of Dr. Sundel and report from Institute of Medicine); Tosches v. Sec'y of Health & Human Servs., No. 06-192V, 2008 WL 440285, at *7 (Fed. Cl. Spec. Mstr. Jan. 31, 2008) (relying upon testimony of Dr. McCusker); Stevens v. Sec'y of Health & Human Servs., No. 99-594V, 2006 WL 659525, at *14 (Fed. Cl. Spec. Mstr. Feb. 24, 2006) (testimony of Prof. Dunbar). The relative resemblance of the two events would seem to contribute to the strength of the challenge-rechallenge paradigm. For example, if a person developed a rash one week after receiving one vaccine and if the person had a seizure one week after receiving the second dose of this vaccine, the rash and seizure might have different etiologies.

Dwelling on the nuanced points of challenge-rechallenge seems unnecessary in this case. The Sanchezes have not established the challenge aspect. As explained above, the Sanchezes have not presented preponderant evidence that Trystan suffered any neurologic problem within at least one month of the February 5, 2009 vaccine. And, by simple definition, without a "challenge," there can be no "rechallenge."

Moreover, to the extent that similarity in reaction can be considered in an analysis of challenge-rechallenge, the Sanchezes' argument weakens even further. The Sanchezes have alleged that following the first DTaP vaccination, Trystan reacted acutely by crying inconsolably, running a fever, and developing a red spot on his thigh. But, there appears to be no persuasive evidence that Trystan suffered any type of acute reaction to the second DTaP vaccination. The Sanchezes have not offered any explanation for why an agent that produced (in their view) a sharp response on Trystan's first encounter would produce a much different response on the second encounter.

In advancing their challenge-rechallenge argument, the Sanchezes have cited reports from doctors who obtained histories about Trystan much later. See Pet'rs' Remand Br. at 32-33 (citing exhibit 1 at 196 (Dr. Friedman's August 2, 2010 report) and exhibit 26 at 8 (Dr. Haas's March 26, 2013 report)). A more detailed analysis of the reports from some treating doctors, including Dr. Friedman and Dr. Haas, is deferred until section VII.C below. However, the undersigned has considered Dr. Friedman's and Dr. Haas's statements in finding that the Sanchezes have not met their burden of proof with respect to challenge-rechallenge. Although Ms. Marin-Tucker observed that Trystan lost developmental abilities in her appointment on October 7, 2009, that decline does not automatically constitute a rechallenge.

The Ruling Finding Facts memorializes the next events in Trystan's history. It states:

> 22. Between October 7, 2009, and his neurology visit on November 12, 2009, Trystan began having "tremors" or "twitching" of his whole body. Tr. at 199-200; Exhibit 1 at 140.
>
> 23. On November 12, 2009, Trystan was taken to see Dr. David J. Michelson, the neurologist to whom he was referred. Dr. Michelson recorded reports that Trystan was unable to sit independently, his hands stayed closed, and his feet went forward when at rest. He noted that, at times, Trystan could hold his mouth open tightly and drool, but at other times he could chew and swallow well. While Trystan had previously held his right arm stiffly behind him episodically, he had not done this lately. Dr. Michelson's review of systems was positive for muscle spasms, global developmental delay, weakness, walking problems, constipation and birthmarks. Dr. Michelson noted that Trystan suffered from "global developmental delay of unclear etiology, though a genetic predisposition is suspected based on the family history and a [central nervous system] cause is suggested by the physical exam findings." Exhibit 1 at 140-41.

Ruling Finding Facts ¶¶ 22-23. Dr. Michelson ordered an MRI, which Trystan underwent in December 2009. The MRI showed problems in Trystan's basal ganglia. Exhibit 1 at 142; see also id. at 130 (reinterpretation of same study). A

problem in the basal ganglia is often found in people suffering from Leigh's syndrome. See Tr. 407, 2126.

The doctors spent several years trying to determine what condition was afflicting him. Finally, during this litigation, the Sanchezes obtained genetic testing for Trystan. Exhibits 53 and 59. These tests showed that Trystan suffered two mutations. Whether these mutations caused Trystan's Leigh's syndrome is discussed in section VIII below.

In sum, this section B has considered both how the Sanchezes' experts predicted an adverse reaction to the vaccination would appear and how Trystan actually appeared. Because of the dichotomy between the predicted and the actual, the sequence of events is not logical. Thus, the Sanchezes have not met their burden regarding prong 2.

C. Treating Doctors

With respect to Althen prong 2, the Federal Circuit has instructed special masters to consider carefully the views of a treating doctor. Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1326 (Fed. Cir. 2006). However, the views of a treating doctor are not absolute. Snyder v. Sec'y of Health & Human Servs., 88 Fed. Cl. 706, 745 n.67 (2009).

The Sanchezes argue that treating doctors have indicated that the vaccination caused Trystan's problems. They list four doctors. Pet'rs' Remand Br. at 29. For the reasons explained below, they overstate the significance of these reports.

Dr. Friedman. In 2010 and 2011, Dr. Friedman stated that Trystan might have acute disseminated encephalomyelitis. Thus, she suggested that Trystan could have "ADEM secondary to vaccine" and "other vaccine toxicity." Exhibit 10 at 7 (Sept. 6, 2011).[40]

If Trystan suffered from ADEM, then Dr. Friedman's opinion could be quite valuable. However, Trystan does not have ADEM. Genetic testing shows that he has Leigh's syndrome. Thus, Dr. Friedman's report does not advance the Sanchezes' claim that the vaccinations contributed to Trystan's Leigh's syndrome.

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[40] DTaP and other vaccines have been found to cause ADEM. E.g., Lerwick v. Sec'y of Health & Human Servs., No. 06-847V, 2011 WL 4537874 (Fed. Cl. Spec. Mstr. Sept. 8, 2011).

Dr. Sharma. Akhil Sharma saw Trystan for a new well-child examination on October 2, 2013. Exhibit 137 at 1. Under "past medical history," Dr. Sharma has recorded that Ms. Sanchez told him Trystan "Did well till 6 mo. Got 6 mo shots for the first time and got fever and seizures [after] that followed by regression of milestones." Id. This "past medical history" concludes: "probable vaccine induced injury." Id. Dr. Sharma repeats this history in his June 26, 2015 medical record. Id. at 8.

Dr. Sharma's reports carry little persuasive value. The record appears to reflect Ms. Sanchez's account of the events in Trystan's life as opposed to Dr. Sharma's evaluation. Even within Ms. Sanchez's recollection, Ms. Sanchez seems to indicate that following the vaccinations when Trystan was six months, Trystan had a "fever and seizures." While Ms. Sanchez may sincerely believe that Trystan had a seizure on the night of February 16, 2009, the record does not persuasively establish that a seizure happened then. Thus, to the extent that Dr. Sharma reached an opinion that Trystan had a "probable vaccine induced injury," Dr. Sharma's conclusion seems to derive from an erroneous starting point. As such, the undersigned gives Dr. Sharma's opinion about the cause of Trystan's neurologic problem little weight. See Dobrydnev v. Sec'y of Health & Human Servs., 566 F. App'x 976, 983 (Fed. Cir. 2014) (noting special master may reject the testimony of a doctor who examined the vaccinee when the doctor receives an inaccurate history); Castaldi v. Sec'y of Health & Human Servs., 119 Fed. Cl. 407, 416 (2014) (determining that special master was not arbitrary in considering that the reports from a treating doctor "were largely based on [the petitioner's] recollection rather than [the doctor's] own observations"); Balasco v. Sec'y of Health & Human Servs., No. 17-215V, 2020 WL 1240917, at *21 (Fed. Cl. Spec. Mstr. Feb. 14, 2020) (rejecting statements from treating doctors about diagnosis when the treaters relied upon history that was not correct).

Dr. Haas. Dr. Haas first saw Trystan on August 7, 2012. Exhibit 26 at 1. The date of this first visit was approximately three months after the onset hearing at which Trystan's family members testified. The history that Dr. Haas obtained is similar to the testimony the family provided during that hearing. Dr. Haas recorded:

> Trystan was perfectly normal until 6 month vaccines. Parents report he was saying mama, dada and supporting weight on his legs at that time. Parents didn't do 2 month or 4 month shots, then showed up for 6 month vaccines at 5 mo of age. (at this visit noted to have normal development, rolling back to front

> and standing when placed, passing objects hand to hand and rake sand grasping small objects, sitting with support, no head leg [sic "lag" may have been intended] with pull to sit) Got his shots, then shortly developed fever and cranky. Then developed congestion (1-2 weeks after). Were giving him Tylenol. Saw PMD, Dx otitis media, gave Amox. The fever persisted and he had inconsolable crying. 11 days after the vaccination, he had an episode of 'contortion' in the upper limbs. He would stiffen his arms behind his back, he would jerk his arms and his neck, sometimes at same time, sometimes one after another. No loss of consciousness. Would do this minutes at a time. Dad would try to straighten his arms but they would snap back. He would do this when awake and asleep. No post-ictal.

Exhibit 26 at 1. With respect to immunizations, Dr. Haas recorded: "Not up to date. . . . Got sick (cough, fever, congestion) right after his second set, and then started having seizures." Id. at 2. After obtaining additional information and conducting a physical exam, Dr. Haas assessed Trystan:

> Trystan is a 4 year old boy who had acute onset regression and dystonia at 6 months of age, following vaccination, which repeated with the next set of vaccines at 12 months.[41] The developmental regression reached a plateau soon after, and he is making some developmental progress ever since. The dystonia persists, with truncal hypotonia. He has basal ganglia abnormalities on his MRI scan, and abnormally raised CoQ and Complex IV in his muscle. The next step would be for his muscle to be sent for mtDNA sequencing. We will search for stored muscle.

Id. at 3.

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[41] The basis for Dr. Haas's statement that something "repeated with the next set of vaccines at 12 months" is not readily apparent as the history that Dr. Haas obtained does not refer to anything happening after Trystan's vaccinations at 12 months.

The Sanchezes emphasize that Dr. Haas wrote that the onset of Trystan's regression and dystonia came "following vaccination." Pet'rs' Remand Br. at 29.[42] Dr. Haas retained this wording in subsequent records as well. See exhibit 26 at 8 (Mar. 26, 2013); exhibit 52 at 1-2 (June 10, 2014).

On its face, a statement that the illness occurred "following vaccination" presents a sequence of events. The recitation of a chronological sequence of events is not the same as an opinion regarding causation. See Cedillo v. Sec'y of Health & Human Servs., 617 F.3d 1328, 1347-48 (Fed. Cir. 2010); La Londe v. Sec'y of Health & Human Servs., 110 Fed. Cl. 184, 206 (2013), aff'd on other ground, 746 F.3d 1334 (Fed. Cir. 2014); Langland v. Sec'y of Health & Human Servs., 109 Fed. Cl. 421, 439 (2013) (stating that the special master was not arbitrary in finding that the records from treating doctors "reflect no more than intake histories or temporal associations"); Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 139-40 (2011), aff'd without op., 463 F. App'x 932 (Fed. Cir. 2012).

Furthermore, these three statements from Dr. Haas came before the genetic mutations in Trystan were discovered. After the genetic mutations were identified, Dr. Haas wrote a letter to other medical providers. Dr. Haas told Trystan's other doctors that "Trystan Evan Sanchez has a mitochondrial disease caused by Complex II deficiency of the respiratory chain. This is a genetic disease causing in Trystan dystonia, developmental delay, encephalopathy, neuromuscular disease[, and an] abnormal MRI." Exhibit 62 at 6. Here, Dr. Haas does not state that the cause of Trystan's disease was the vaccination.

Yet, Dr. Haas does not completely ignore the vaccinations. In a September 24, 2019 report, Dr. Haas stated that Trystan has "Leigh's disease due to complex II deficiency . . . This boy's mitochondrial disease is life threatening and he can deteriorate with stress situations including the possibility of fever after immunization. For this reason it is medically acceptable for him to avoid immunizations." Exhibit 184 at 53.

A recommendation to avoid vaccinations is not necessarily the same as a statement that a vaccine caused an injury. See Moberly v. Sec'y of Health & Human Servs., 85 Fed. Cl. 571, 604-05 (2009), aff'd, 592 F.3d 1315 (Fed. Cir.

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[42] The Sanchezes also cite exhibit 53. However, exhibit 53 is not a report from Dr. Haas. Exhibit 53 is a GeneDx report, dated November 5, 2014.

2010); Rickard v. Sec'y of Health & Human Servs., No. 09-729V, 2011 WL 1979601, at *12 (Fed. Cl. Spec. Mstr. Apr. 11, 2011) (indicating that the doctor recommended avoiding future vaccinations as part of a standard practice).

Dr. Wong. Upon referral from Dr. Sharma, Derek Wong from the Children's Hospital of Los Angeles, division of medical genetics, saw Trystan on January 28, 2016. In his history, Dr. Wong states that he is quoting a record from Dr. Haas:

> He had vaccines at five months of age, then had fever and irritability. He developed congestion, and had a fever and otitis [media]. 11 days after the vaccines, he had stiffening episodes that lasted for 18 months.[43] After this episode, he lost head control but regained it 1-2 months later.

Exhibit 139 at 1. The history in Dr. Wong's report continues:

> At 12 months of age, Trystan had some intermittent rigidity of his extremities, head lag, and significant developmental delay. [Ms. Sanchez] told me that he had vaccines at 12 months of age that caused further developmental regression although I am unclear on the sequence of events after reading Dr. Haas's notes. That note states that the patient had cough, fever, and congestion after his 12 month immunizations, and that seizures started after that point.

Id. at 1.[44]

Dr. Wong reviewed the results from other tests including the whole exome sequencing showing the c.667delG and c.1571C>T mutations. According to Dr. Wong, "[t]herefore the diagnosis of complex II deficiency secondary to SDHA mutations was made, and specifically Leigh syndrome." Id. at 2. When Dr. Wong reviewed Trystan's immunization status, Dr. Wong recorded: "Immunizations are

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[43] The basis for Dr. Wong's January 2016 statement that Trystan had stiffening for 18 months is not readily apparent.

[44] Rather than quoting Dr. Haas's records, Dr. Wong appears to be significantly paraphrasing the records. See exhibit 26 at 1-2.

not up to date. Note possible reactions to vaccines – developmental regression." Id. at 3.

All this description of Trystan's condition precedes the passage that the Sanchezes quote. Pet'rs' Remand Br. at 75. In Dr. Wong's assessment, he states Trystan's "manifestations include developmental regression, following vaccines and/or viral syndrome." Exhibit 139 at 5. However, the Sanchezes do not point out that in the previous sentence, Dr. Wong wrote, "Trystan is a 7 year old male with mitochondrial complex II deficiency secondary to compound heterozygous mutations in the succinate dehydrogenase A (SDHA) gene." Id.

Dr. Wong's record provides little assistance to the Sanchezes. At best, like Dr. Haas and Dr. Sharma, Dr. Wong recognizes a temporal sequence in which Trystan's developmental regression "follow[ed] vaccines and/or viral syndrome." But, even this statement from Dr. Wong must be placed in the context in which Dr. Wong describes Trystan's developmental regression as a "manifestation" of a "mitochondrial complex II deficiency secondary to compound heterozygous mutations."

In summary, the records from four doctors who treated Trystan do not help the Sanchezes meet their burden of showing that the DTaP vaccination contributed to Trystan's Leigh's syndrome. Dr. Friedman presented her opinion before Trystan's Leigh's syndrome was diagnosed after genetic studies. Dr. Sharma and Dr. Haas obtained histories that are not entirely accurate. Even so, Dr. Sharma, Dr. Haas, and Dr. Wong appear to present temporal sequences. Accordingly, while these reports have been considered, they do not constitute persuasive evidence for the Sanchezes.

VIII. Genetics

The previous sections (V, VI, and VII) constitute the Althen analysis and for the reasons explained therein, the Sanchezes have not met their burden of proof and, therefore, are not entitled to compensation. Nevertheless, the Secretary presented an alternative and independent explanation for finding that the Sanchezes are not entitled to compensation—Trystan's genetic mutations.

Like many sections in this remand decision, this section begins with a summary of the procedural posture (section A) because those steps are the basis for determining the scope of remand (section B). Then, section C sets forth the burdens with respect to alternative factors. Information about Trystan's genetics, the parties' arguments, and a summary of the most important articles are developed

in sections D, E, and F, respectively. Finally, section G presents the reasons for finding that the mutations constitute the sole substantial cause of Trystan's Leigh's syndrome.

A. Procedural History regarding Genetics

As noted earlier, Trystan was tested for genetic mutations during this litigation and the testing showed that he possessed two mutations. The testing company, GeneDX, described both mutations as pathogenic. Exhibit 53.

The discovery of the genetic mutations added another aspect to the Sanchezes' claim that the vaccination harmed Trystan. The Sanchezes brought in Dr. Niyazov because he has expertise in mitochondrial disorders. Dr. Niyazov opined that the genetic mutation only predisposed Trystan to developing Leigh's syndrome and the vaccination caused this disposition to become a reality. Exhibit 68. Dr. Steinman, too, expressed a similar opinion, although the Sanchezes rely less upon Dr. Steinman. Exhibit 95. The Secretary's expert, Dr. Raymond, who, like Dr. Niyazov, is board-certified in genetics opined that "Trystan Sanchez is a child with Leigh syndrome secondary to mutations in the gene SDHA. This is the sole cause of his neurologic condition." Exhibit H at 8. The parties continued to develop their points through additional expert reports, briefing in advance of the hearing, and oral testimony during the December 2017 hearing.

The October 9, 2018 decision found that the Sanchezes did not meet their burden of proof regarding Althen prongs 2 and 3. Thus, they were not entitled to compensation. However, because the parties had invested so much into the genetics issue, the undersigned offered additional views regarding the genetics aspect of the case. The undersigned concluded that "Trystan's actual course is entirely consistent with what is known about his genetic mutations." Decision at 41, 2018 WL 5856556, at *25.

Following the decision, the Sanchezes filed a motion for review. The Sanchezes, however, did not present any argument regarding Trystan's genetics. Rather, on the thirty-ninth and final page of their motion, the Sanchezes asserted that "[t]he perceived errors in this part of the Decision are not addressed in this Motion. Petitioner[s] reserve[] the right to [do] so in the event the issue comes to the forefront." Pet'rs' Mot. for Rev. at 39 n.34. The Secretary did not present any argument regarding genetics. See Resp't's Resp. to Mot. for Rev. The Reply, too, was silent on this issue. See Pet'rs' Reply in Support of Mot. for Rev. The Court's Opinion and Order denied the motion for review without commenting on the genetics. See Opinion and Order.

The parties' briefs to the Federal Circuit were similar. Although the Sanchezes' initial brief did not discuss the comments in the October 9, 2018 decision regarding genetics, in their reply brief, the Sanchezes presented essentially the same footnote as they used in their motion for review. Again, the Sanchezes maintained that they "reserve[] the right to [address perceived errors in the Decision regarding genetics] in the event the issue comes to the forefront." Reply of Appellants-Petitioners at 29 n.12.

During oral argument, a member of the Federal Circuit panel inquired whether the Secretary was defending the October 9, 2018 decision on the basis of the genetics. The Secretary stated that he was not.[45]

The Federal Circuit vacated the judgment based upon the October 9, 2018 decision because of errors in the Althen analysis. In remanding for correction of these errors, the Federal Circuit permitted additional findings on the genetics issue:

> Finally, it may be necessary for the special master to address a question that was left open in the last two pages of the special master's decision denying compensation: whether the Secretary showed, because of Trystan's mutations, the timing and severity of his Leigh's syndrome would have been the same, regardless of the effect of the vaccinations.

Sanchez, 809 F. App'x at 854. The Federal Circuit also stated that the special master could "give the parties an opportunity to supplement the record with any relevant medical research or reports postdating the hearing held by the special master two and one-half years ago." Id.

On remand, the undersigned allowed the parties to present additional reports, see order, issued June 12, 2020, and the parties did so, addressing genetics along with other issues. E.g., exhibits 189, 195 (both Dr. Niyazov), P, Q (both Dr. Raymond). The parties' experts also discussed genetics during the July 9, 2020

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[45] Oral Argument at 17:07-17:43, Sanchez v. Sec'y of Health & Human Servs., 809 F. App'x 843 (2020) (No. 2019-1753), http://www.cafc.uscourts.gov/oral-argument-recordings?title=Sanchez&field_case_number_value=2019-1753&field_date_value2%5Bvalue%5D%5Bdate%5D=2020-02-07; see also Pet'rs' Remand Br. at 67, 89.

hearing. After the hearing, the parties made arguments regarding genetics in their briefs.

B. Scope of Remand

Notwithstanding the Federal Circuit's invitation to consider the genetics issue, the Sanchezes argue that the undersigned cannot evaluate this evidence on remand. They maintain, "The genetics portion of the Special Master's decision made it clear that it was not how the [special master] decided the case. Therefore, it was not part of any appeal. The law of the case doctrine applies. Respondent did not rely on this portion of the Decision at either the Motion for Review or the Federal Circuit Appeal." Pet'rs' Remand Br. at 89; accord Pet'rs' Reply on Remand at 20.

However, the Sanchezes appear to misapprehend the law of the case doctrine. A trial court's failure to rule on one claim or defense does not create a waiver for the party advancing the claim or defense. See Exxon Chem. Patents, Inc. v. The Lubrizol Corp., 137 F.3d 1475 (Fed. Cir. 1998) (an appellate conclusion that a party did not literally infringe a patent does not prevent the plaintiff from seeking a new trial under the doctrine of equivalents); Laitram Corp. v. NEC Corp., 62 F.3d 1388, 1395 (Fed. Cir. 1995) (reinstating a jury's verdict decided on literal infringement and the doctrine of equivalents grounds, based only on the appellate determination of error with respect to the literal infringement claim and without reaching the doctrine of equivalents issue).

C. Burdens regarding Alternative Factor

When petitioners carry their burden to show that a vaccine was the cause-in-fact of an injury, the Secretary may rebut this showing by establishing that the injury is "due to factors unrelated to the administration of the vaccine." 42 U.S.C. § 300aa–13(a)(1)(B).[46] For the government to carry its burden, "the Secretary refutes the prima facie finding that the vaccination is both the 'but for' cause and a 'substantial factor' in bringing about an alleged injury. . . . Because the factor unrelated must be the 'sole substantial factor,' the Secretary must establish that the factor unrelated, not the vaccination, actually caused the injury alleged." Deribeaux v. Sec'y of Health & Human Servs., 717 F.3d 1363, 1369 (Fed. Cir.

[46] Because the Sanchezes have not met their burden to show that the DTaP vaccine contributed to Trystan's injury, the burden of proof actually never shifted to the Secretary. However, the following analysis assumes that the Sanchezes met their burden of proof.

2013). The Secretary's burden with respect to alternative causation is "the same as" the standards for "petitioner's proof of actual causation in fact in off-table cases." Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 549 (Fed. Cir. 1994). And, the petitioner's burden is preponderance of the evidence. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

The Sanchezes argue that the Secretary's burden to establish an alternative factor as the cause of an injury is greater than a petitioner's burden to establish causation-in-fact. For this proposition, the Sanchezes rely upon de Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1351-54 (Fed. Cir. 2008). Pet'rs' Remand Br. at 10-11, 74-75; Pet'rs' Reply on Remand at 16-17.

In that case, Adela Quintana de Bazan received a tetanus-diphtheria vaccine and within eleven hours developed symptoms of a neurologic disease, acute disseminated encephalomyelitis (ADEM). 539 F.3d at 1349-50. After a hearing, the special master credited the Secretary's expert who had opined that eleven hours was too short to infer causation. On a motion for review, a judge of the Court of Federal Claims "held that the special master had erred by improperly failing to shift the burden to the government. The court held that the finding that the eleven-hour onset of ADEM was not within a medically appropriate timeframe to attribute to the vaccine was tantamount to finding that de Bazan had failed to prove that no other cause could have caused her injuries." Id. at 1350. After remand in which the Secretary presented no new evidence, the special master found in favor of the petitioner. The Secretary then appealed the judgment to the Federal Circuit.

The Federal Circuit reversed. The Federal Circuit stated, "the court misunderstood our precedents." Id. at 1353. The Federal Circuit held that in requiring Ms. de Bazan to show her ADEM arose in an appropriate amount of time after the vaccination, the special master did not impose an additional burden on her. In this context, the Federal Circuit stated that after a petitioner meets her burden under Althen, "The government then must provide that [contrary] proof by identifying a particular such factor (or factors) and presenting sufficient evidence to establish that it was the sole substantial factor in bringing about the injury." Id. at 1354. However, the Federal Circuit was not called upon to address dimensions of the "sole substantial factor" as the Secretary had not presented any evidence regarding a factor unrelated to the vaccine. Id.

The Federal Circuit has ruled that a special master's finding that a genetic mutation was the "sole substantial factor" to cause a child's disease satisfies the respondent's burden in showing that the injury was due to factors unrelated to the

vaccine. See Deribeaux v. Sec'y of Health & Human Servs., 717 F.3d 1363 (Fed. Cir. 2013); Stone / Hammitt v. Sec'y of Health & Human Servs., 676 F.3d 1373 (Fed. Cir. 2012) (separate cases considered together on appeal); see also Snyder v. Sec'y of Health & Human Servs., 553 F. App'x 994 (Fed. Cir. 2014). While the children in all three cases[47] had a mutation in the SCN1A gene, the most analogous case is Stone / Hammitt.

When Rachel Hammitt was approximately four months old, she received a dose of the DTaP vaccine and several other vaccines. That evening, she experienced a febrile seizure for which she remained hospitalized for several days. About one month later, Rachel had a second seizure and was again treated in the hospital. Because of repeated seizures, she was diagnosed with epilepsy by her first birthday. Testing later showed she has a mutation in the SCN1A gene. Stone, 676 F.3d at 1375.

The petitioner in both Stone and Hammitt relied upon an opinion from Marcel Kinsbourne.[48] "A key component of Dr. Kinsbourne's theory is that the initial seizure caused some form of lasting brain injury that had downstream consequences for both children, specifically a lowered seizure threshold. Accordingly, the special master sought evidence of brain damage resulting from the initial febrile seizures." Id. at 1384. The petitioners failed to establish their cases because "Dr. Kinsbourne was unable to identify any evidence that either child had suffered brain damage as a result of those seizures." Id. Thus, on remand, the special master found the petitioner in Hammitt "had not made a prima facie case." Id. at 1378. On appeal the Federal Circuit ruled that the special master's determination was not arbitrary because the petitioners "failed to show that the vaccines caused any brain damage." Id. at 1384.

The special master also found primarily based upon the testimony of Dr. Raymond, that "respondent proved by a preponderance of the evidence that [the] SCN1A gene mutation was the sole cause and was principally responsible for [the child's disease]." Id. at 1378-79 (second alteration added, and citation omitted). At the Federal Circuit, the appellants-petitioners challenged a reliance on Dr.

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[47] Actually, five children because the Federal Circuit consolidated two cases in Stone and Snyder.

[48] The special master expressed concerns about Dr. Kinsbourne's reliability because he has not practiced pediatric neurology since 1981. This weakness in Dr. Kinsbourne's background is not a problem for Doctors Steinman and Niyazov.

Raymond's opinion. However, the Federal Circuit found that the special master was not arbitrary in relying upon Dr. Raymond because, in part, Dr. Raymond considered multiple factors for finding that the SCN1A mutation was the sole cause of the children's seizure disorder. Those factors were:

> (1) the gene mutation was not inherited but arose de novo, so the absence of SMEI in either parent was not probative; (2) the mutation resulted in a non-conservative amino acid change, i.e., the mutation produced a new amino acid having very different physical properties from the corresponding amino acid found in normal individuals; (3) the mutation affects a functionally important region, a portion of the sodium channel in neurons that is crucial to the normal functioning of the nervous system; (4) the mutation occurs in an area that is well conserved across species, "indicating that changes here are probably not well tolerated"; (5) there is an absence of the mutation in the normal population; (6) medical reports show that a mutation in the same location has been associated with SMEI; and (7) between 80 and 90 percent of patients with SMEI have an SCN1A gene mutation.

Id. at 1383. The Federal Circuit stated that based upon this evidentiary support, "we cannot conclude that the special master's conclusion that the SCN1A gene mutation was solely responsible for [Amelia Stone's] SMEI was arbitrary or capricious." Id. at 1384.

Here, the Sanchezes give little recognition to the SCN1A cases, saying, without elaboration, that their case is "unlike" the SCN1A cases. Pet'rs' Remand Br. at 76. Rather, the Sanchezes emphasize a precedential opinion that the Federal Circuit issued while their case was on remand, Sharpe v. Sec'y of Health & Human Servs., 964 F.3d 1072 (Fed. Cir. 2020).[49]

Heidi Sharpe, the mother of L.M., noticed her daughter having episodes of "spacing out" during which L.M. was not responsive for several seconds when she

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[49] While the Secretary was invited to comment upon Sharpe, the Secretary stated, "the Federal Circuit has not yet issued its mandate in Sharpe; accordingly, it is premature for the parties to be speculating about the potential effect of the Sharpe panel's decision." Resp't's Remand Br. at 25.

was approximately five months old. Id. at 1076. At six months old, L.M. received a series of vaccination, including the DTaP vaccine. Later that evening, L.M. was lethargic, had poor muscle tone, and did not eat. L.M.'s mother called the hospital's emergency room twice and her pediatrician later that morning. According to L.M.'s mother, for the next three days, L.M. remained lethargic, had poor head control, and did not interact with her environment. Id. Five days after vaccination, L.M. had a seizure for which she was brought to the hospital. Doctors stated that she had "fairly poor head control." Id. She was diagnosed with infantile spasms. At some point, a genetic mutation was discovered.

L.M.'s mother alleged that L.M. had a pre-existing seizure disorder and the vaccines significantly aggravated it.[50] Under this cause of action, Ms. Sharpe is required to establish the six elements first enumerated in Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009). Sharpe, 964 F.3d at 1080. The special master found that Ms. Sharpe had failed to establish elements 3 (a significant aggravation of the prior condition), 4 (a medical theory), and 5 (a logical sequence of cause and effect). The special master also found that L.M.'s "gene mutation, and not the vaccination, was the sole, substantial cause of L.M.'s significantly aggravated seizure disorder." Id.

The Federal Circuit ruled that the special master erred on all four points. For the Sanchezes' case, the most important comments from the Federal Circuit include a holding that petitioners do not bear the burden of establishing that the vaccinee's current condition is worse than the normal and expected course of the underlying disorder. The Federal Circuit also quoted testimony from the Secretary's witness that "[t]he dream of the geneticist is to find genotype-phenotype correlation." Id. at 1082 (citation omitted). The Federal Circuit also found that the special master's finding that the genetic mutation was the likely sole substantial factor causing L.M.'s severe seizure disorder was not supported by substantial evidence. The record did not support the special master's conclusion because the specific mutation in L.M. "generally result[s] in non-severe, non-cognitive disorders." Id. at 1086. For these reasons (and more), the Federal Circuit vacated the judgment based upon the special master's decision.

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[50] Ms. Sharpe also alleged that L.M. experienced a significant aggravation of her seizure disorder due to the DTaP vaccine and claimed compensation as an on-Table injury. The special master denied compensation on that theory and the Federal Circuit affirmed for reasons not relevant to the Sanchezes' case.

D. Trystan's Genetic Mutations

During initial entitlement proceedings, the Sanchezes introduced evidence of Trystan's specific genetic mutations. The October 9, 2018 decision articulated these genetic mutations as follows:

> Trystan inherited two heterozygous mutations in his SDHA gene. Because of the nature of the mutations and their effect on the SDHA protein, the mutations are considered pathogenic. The parties dispute whether these two mutations made Trystan's disease a *fait accompli*.
>
> To understand the potential effect of Trystan's inherited mutations on Trystan's clinical course, it is important to review Trystan's specific mutations and what is known about them.
>
> Trystan's two mutations in his DNA are referred to as c.1571C>T and c.667delG. Exhibit 59 at 1. The first indicates that at location 1571 in the gene, a cytosine (C) has been replaced by a thymine (T). The second indicates that a guanine (G) that is supposed to be present at position 667 has been deleted. In the case of the first, this mutation changes the nucleic acid code so that where there is supposed to be an alanine in the protein, the cell now puts a valine (p.Ala524Val). In the case of the second, the mutation changes the nucleic acid sequence in a manner that creates a premature stop signal in the place of a signal for an amino acid. In other words, the cell believes that no more of the nucleic acid chain needs to be translated into amino acid, resulting in a shortened, or truncated, protein (p. Asp223IlefsX3).

Decision at 31, 2018 WL 5856556, at *19.

E. Overview of Parties' Positions regarding Genetics

The Secretary maintains that "[t]he onset and progression of Trystan's unfortunate condition is entirely explained by what is currently known about Leigh's syndrome generally and Trystan's gene mutations specifically." Resp't's Remand Br. at 26. The Secretary's position comes from the opinion of Dr. Raymond, who relies primarily on the Parfait article, which is discussed below.

Primarily through the opinion of Dr. Niyazov, the Sanchezes maintain that Trystan's genetic mutations were not sufficient, by themselves, to cause him to suffer Leigh's syndrome. Trystan's genetic mutations would cause Leigh's syndrome only after a stressful event, which was his vaccination. See Pet'rs' Remand Br. at 68.[51] Dr. Niyazov relies primarily upon the Levitas article.

F. Important Articles regarding Mutations

In the October 9, 2018 decision, the undersigned outlined and summarized relevant articles presented by the parties as follows:

> Exhibit H, tab 7 (Thomas Bourgeron et al., Mutation of a Nuclear Succinate Dehydrogenase Gene Results in a Mitochondrial Respiratory Chain Deficiency, 11 Nature 144-49 (1995)) presents the first account of a mutation in SDHA being associated with a mitochondrial disease in humans. In this study, the authors reported that two sisters both had a homozygous mutation in SDHA (c.1684 C>T) and that both sisters developed Leigh's syndrome at 10 months of age. One died at 19 months and another was still alive at 13 months.
>
> Exhibit 110 (Beatrice Parfait et al., Compound Heterozygous Mutations in the Flavoprotein Gene of the Respiratory Chain Complex II in a Patient with Leigh Syndrome, 106 Human Genetics 246-43 (2000)) presents a case study of a child with Leigh's syndrome who, like Trystan, had a compound heterozygous mutation of her SDHA gene. The child in Parfait shared one of his two mutations with Trystan (c.1571 C>T). However, the other mutation was distinct between the two children. Little is known about the course of the disease for the young child presented in the Parfait article, other than that she presented with Leigh's syndrome at 9 months of age, demonstrating psychomotor delays and cerebellar ataxia. The authors in the Parfait article took the additional step of showing

[51] The Sanchezes state that the approximately three weeks between the conclusion of the hearing and the deadline for the submission of their initial brief constituted an "[i]nsufficient time . . . to outline in full all of the reports and testimony by Dr. Niyazov regarding the gene mutations[,] the variable expressivity[,] and partial expressivity." Pet'rs' Remand Br. at 70. However, their argument spans many pages. See id. at 66-82, 89-90.

that the reduced functioning of the young child's SDH protein was attributable to the c.1571C>T mutation (the mutation Trystan had), confirming the mutation's pathogenicity.

Exhibit 94 (Rudy Van Coster et al., Homozygous Gly555Glu Mutation in the Nuclear-Encoded 70 kDa Flavoprotein Gene Causes Instability of the Respiratory Chain Complex II, 120A Am. J. Medical Genetics 13-18 (2003)) presents the case study of a young child with a homozygous mutation in the SDHA gene (c.1664 G>A) whose symptoms developed at five months of age and then died two weeks later following a respiratory infection. Though the child may have had Leigh's syndrome, she "died in infancy before any sign of Leigh syndrome could develop." Id. at 4.

Exhibit H, tab 28 (R. Horvath et al., Leigh Syndrome Cased by Mutations in the Flavoprotein (Fp) Subunit of Succinate Dehydrogenase (SDHA), 77 J. Neurology Neurosurgery Psychiatry 74-76 (2006) presents the case of a young girl with a compound heterozygous mutation in her SDHA gene. Her two mutations were not seen in any other study. The patient first showed signs of Leigh's syndrome at five-months of age. While she had reached 10 years at the time the study was published, she had also shown an arrest of her psychomotor development and experienced recurrent seizures.

Exhibit H, tab 27 (Alistair T. Pagnamenta et al., Phenotypic Variability of Mitochondrial Disease Caused by a Nuclear Mutation in Complex II, 89 Molecular Genetics and Metabolism 214-21 (2006)) presents the case of a young boy with the exact same mutations presented in exhibit 94 (Van Coster). However, in contrast to the patient described in Van Coster, the patient in Pagnamenta did not develop symptoms of Leigh's syndrome until 22 months of age. While his onset was rapid, he began showing an improved clinical picture after turning four. At the time the article was published, the child was 10 years old and showed variably impaired motor function, but did not appear to manifest any cognitive deficits and attended a mainstream school.

> Exhibit 79 (Aviva Levitas et al., Familial Neonatal Isolated Cardiomyopathy Caused by a Mutation in the Flavoprotein Subunit of Succinate Dehydrogenase, 18 European J. Human Genetics 1160-65 (2010)) is the most recently published article in the record concerning the significance of SDHA mutations. The Levitas article is unique for two reasons. First, the authors presented an examination of fifteen individuals from two large consanguineous families, allowing for better discrimination about the penetrance of the mutation. Second, the patients did not present with Leigh's syndrome. Instead, with the exception of one patient, the subjects had, or had died of, cardiomyopathies of various severities. The onset of the disease, or death, occurred at earlier than one year of age in all the children studied. This is all the more fascinating because the mutation involved in Levitas was the same exact mutation that was associated with Leigh's syndrome in Van Coster and Pagnamenta. Nonetheless, not a single family member developed Leigh's syndrome. Even more, at least one patient, the father, who had the homozygous mutation that was also present in Van Coster and Pagnamenta (c.1664 G>A), had no symptoms of disease at all. This astonished the researchers and they performed several follow-up studies to try to explain this finding, though they had no success. Importantly, it was confirmed that this patient had a loss of function of the SDH gene, much as was the case in Parfait, but nonetheless did not develop any disease.

Decision at 31-33, 2018 WL 5856556, at *19-20.

In December 2017, when Dr. Niyazov and Dr. Raymond testified, Trystan's second mutation (the c.667delG mutation) had not been reported in the literature. Tr. 2089. With the passage of time, doctors have reported this mutation in the context of epilepsy and paraganglioma tumors. Exhibit 189 (Dr. Niyazov's June 19, 2020 report) at 2; see also exhibit P (Dr. Raymond's June 19, 2020 report) at 5.[52]

[52] Dr. Raymond did not note the appearance of the c667delG mutation in epilepsy and paraganglioma tumors. See exhibit P. Given that this oversight was brought up during his

G. Evaluation of the Genetic Evidence

After discussing pathogenicity and penetrance, the October 9, 2018 decision found that "Trystan's actual course is entirely consistent with what is known about his genetic mutations." Decision at 41, 2018 WL 5856556, at *25. However, the undersigned did not make an explicit finding as to whether the genetic mutations were the sole substantial cause of Trystan's Leigh's syndrome.

The undersigned now finds that Trystan's mutations were the sole substantial cause of his Leigh's syndrome. While the reasons for this finding are presented below, the undersigned first explains why this finding is being made now, as opposed to October 2018.

The October 9, 2018 decision did not require a finding with respect to the genetics issue. It was sufficient to find that the Sanchezes did not carry their burden regarding Althen prong 2 and Althen prong 3. When special masters can resolve a case a based upon one issue, they do not necessarily need to address all issues. See, e.g., Hibbard v. Sec'y of Health & Human Servs., 698 F.3d 1355, 1365 (Fed. Cir. 2012); Vaughan v. Sec'y of Health & Human Servs., 107 Fed. Cl. 212, 222 (2012).

It is still correct that the genetics issue is an alternative basis for denying compensation to the Sanchezes in that, even after consideration of the arm contortions, they have not met their burdens regarding Althen prong 2 and Althen prong 3. See sections VI and VII above. Nevertheless, under the circumstances of this case, a finding regarding genetics will advance judicial economy because as part of the remand process, the undersigned has re-reviewed the evidence regarding genetics.

Dr. Niyazov has made some points regarding the incomplete penetrance of some SDHA genetic mutations. The results from the Levitas article cannot be—and are not—dismissed out of hand.

On the other hand, the Secretary's burden to show that the genetic mutations are the sole substantial cause of Trystan's Leigh's syndrome is a simple preponderance of the evidence. The Secretary does not have to present either a

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testimony, Tr. 2089, 2092-96, 2134-35, 2169, the Secretary's statement that "no clinical information [has been] provided" seems inaccurate. Resp't's Remand Br. at 28.

clear and convincing case or a case beyond a reasonable doubt. The Secretary is only required to tip the metaphorical scales of justice.

The Secretary has carried this burden in this case. Much as he was in Stone, Dr. Raymond was a credible expert. Dr. Raymond's reliability comes, in part, from his reliance on the Parfait paper. As indicated in the title of the article, the child in Parfait suffered from compound heterozygous mutations in the flavoprotein gene of the respiratory chain complex II. "Heterozygous" means that one of the child's parents provided one normal gene and one of the child's parents provided one mutation.[53] "Compound" means that the child suffered two different heterozygous mutations.

Dr. Raymond's reliance on Parfait stems from the similarity in genetic mutations between the Parfait child and Trystan. In both children, the genetic mutation at codon 524 is exactly the same. Tr. 478, 537 (Dr. Niyazov). The second mutation created a premature stop code in the gene, resulting in a shorter protein. Although the details of the second genetic mutation in the Parfait child and Trystan do not match entirely, the end result--a shortened protein—is the same. Tr. 814-15, 980.

After the Parfait researchers discovered the mutations, they explored the significance. With respect to the c.1571C>T mutation, the mutation that Trystan shares, the researchers determined that it was "absent from 150 controls." Beatrice Parfait et al., *Compound heterozygous mutations in the flavoprotein gene of the respiratory chain complex II in a patient with Leigh syndrome*, 106 Hum. Genetics 236, 236 (2000), filed as exhibit 110. The researchers used fibroblasts to see how the gene performed in tissue cultures. Id. at 241; Tr. 539. Their experiment "confirm[ed] the deleterious effect of this mutation." Exhibit 110 (Parfait) at 241. The Parfait researchers did not perform a functional analysis on the second mutation, which may result in a shortened protein. Tr. 995. However, as Dr. Niyazov recognized, shortened proteins often contribute to disease because the entire protein is not created. Tr. 912-13; see also Tr. 806-07 (Dr. Raymond discussing GeneDx report that truncation mutations are almost always pathogenic).

While Dr. Raymond opined that the Parfait article supported a finding that Trystan's genetic mutations, and solely his genetic mutations, caused Trystan's

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[53] Although Dr. Niyazov maintained that one of the Parfait child's mutations was homozygous, Tr. 489, 978, this interpretation seems to be erroneous. Tr. 1001-02.

Leigh's syndrome, Dr. Niyazov's response to Parfait varied. On the one hand, Dr. Niyazov agreed that Trystan could be compared to the child in Parfait because one of the two mutations (the 524 mutation) was the same. Tr. 488. Dr. Niyazov agreed that the 524 mutation was "deleterious" and an "altering function mutation." Tr. 541, 543. Despite this agreement, Dr. Niyazov would not concede that the mutation caused disease because Dr. Niyazov would "need to see the clinical features of the patient." Tr. 542. He defended his position by citing Levitas.

In the respect of needing to see clinical features of the patient, Dr. Niyazov seems to be demanding a level of scientific certainty that exceeds the preponderance of the evidence standard. Contrary to a question posed by the Sanchezes' attorney during cross-examination of Dr. Raymond, the Parfait article does not represent a case report in which the researchers memorialized an event and an outcome. See Tr. 896-97. While the Federal Circuit in Sharpe warned against relying upon a single case study, Sharpe, 964 F.3d at 1084 (discussing the Ambry patient), the Parfait article is not a simple case report. Instead, the Parfait researchers studied how the gene would be expressed in cell cultures. Exhibit 110 (Parfait) at 241. This experiment strengthens the value of the Parfait article, making it worthy of more weight than case reports, which petitioners in the Vaccine Program often supply. See, e.g., Campbell v. Sec'y of Health & Human Servs., 97 Fed. Cl. 650, 668-69 (2011); Tompkins v. Sec'y of Health & Human Servs., No. 10-261V, 2013 WL 3498652, at *23-24 (Fed. Cl. Spec. Mstr. June 21, 2013), mot. for rev. denied, 117 Fed. Cl. 713 (2014). While Dr. Niyazov may be correct from a scientist's perspective that an in vivo, as opposed to in vitro, experiment may be more informative, Dr. Niyazov has not proposed how an in vivo study could be conducted on the 524 mutation. Furthermore, the Vaccine Program does not demand this level of proof from petitioners when they attempt to establish that a vaccine harmed them. Consequently, the Secretary cannot be held to a standard of proof that requires scientific certainty. Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 549 (Fed. Cir. 1994).

The gene expression studies are conducted, as far as the undersigned is aware, to minimize the contribution, if any, from environmental factors, such as vaccinations. And based upon the gene expression studies in Parfait, Dr. Niyazov appropriately conceded that the researchers had determined that the 524 mutation, which is the mutation Trystan shares with the Parfait child, is an "altered function" mutation. Tr. 543. From this concession that the 524 mutation alters the function of its associated protein, it seems reasonable to conclude that the altered function will lead to a disease, especially when that conclusion is supported by Dr.

Raymond's opinion. From the conclusion that the 524 mutation is likely to cause a disease, it also seems logical to conclude that the specific disease a compound heterozygous mutation involving the 524 gene is likely to cause is Leigh's syndrome because the Parfait child developed Leigh's syndrome.

Additional support for the finding that the 524 mutation in combination with the other mutation caused Trystan's Leigh's syndrome can be found by examining the factors upon which Dr. Raymond relied in Stone.[54]

Factor in Stone	Trystan's case
(1) the gene mutation was not inherited but arose de novo, so the absence of SMEI in either parent was not probative;	Trystan inherited one mutation from each parent. Neither parent had both mutations.
(2) the mutation resulted in a non-conservative amino acid change, i.e., the mutation produced a new amino acid having very different physical properties from the corresponding amino acid found in normal individuals;	Present in Trystan's case. The second mutation produced a shortened protein.
(3) the mutation affects a functionally important region, a portion of the sodium channel in neurons that is crucial to the normal functioning of the nervous system;	The gene expression studies on the 524 mutation in Parfait suggest that the relevant region is crucial.
(4) the mutation occurs in an area that is well conserved across species, "indicating that changes here are probably not well tolerated";	The SDHA gene is highly conserved across species. Tr. 527 (Dr. Niyazov).

[54] By returning to the list of factors in Stone, the undersigned is not suggesting that the list amounts to some sort of legal test. However, given that the Federal Circuit in Stone found Dr. Raymond's ultimate conclusion not arbitrary, the methodology or factors that he considered appear relevant.

(5) there is an absence of the mutation in the normal population;	This appears to be true for Trystan. The Parfait researchers did not find the 524 mutation in 150 controls. See Tr. 909 (Dr. Raymond's testimony about lack of appearance in the normal population), 2169-70 (Dr. Niyazov discussing, in the context of the Parfait article, an absence of cases with Trystan's specific genetic mutations).
(6) medical reports show that a mutation in the same location has been associated with SMEI;	Parfait constitutes a single report (not plural reports) that a compound heterozygous mutation has been reported in Leigh's syndrome. But the c.667delG has not been reported in Leigh's syndrome.
(7) between 80 and 90 percent of patients with SMEI have an SCN1A gene mutation.	Not present.

Thus, most of these seven factors tend to align with a finding that Trystan's compound heterozygous mutation caused his Leigh's syndrome.

While a strength to Dr. Raymond's opinion is that he based his analysis on the genetic mutations that Trystan has, Dr. Niyazov's opinion is relatively weaker because he relies upon Levitas, which reported results on a different genetic mutation. Dr. Niyazov's reliance on Levitas is not irrational for Levitas does illustrate the point that SDHA genes can have variable expressivity. However, Levitas merits less weight than the Parfait article that included a gene expression study on the gene that affects Trystan. In other words, Levitas and Dr. Niyazov's opinion about Levitas and the other articles he has cited might prevent a finding that the Secretary had clearly and convincingly established the genetic mutations as the sole substantial cause. But, the value of Levitas and Dr. Niyazov's opinion is not so strong to defeat a claim based upon a preponderance of the evidence.

In addition, despite receiving inaccurate histories concerning Trystan's health in the months following the vaccination, two doctors have linked Trystan's genetic mutation to his Leigh's syndrome. As noted above, Dr. Wong, a medical

geneticist, stated "Trystan is a 7 year old male with mitochondrial complex II deficiency secondary to compound heterozygous mutations in the succinate dehydrogenase A (SDHA) gene." Exhibit 139 at 5. Dr. Haas also told other doctors that "Trystan Evan Sanchez has a mitochondrial disease caused by Complex II deficiency of the respiratory chain. This is a genetic disease . . . ." Exhibit 62 at 6. These statements reinforce the finding that the pair of genetic mutations is the sole substantial cause for Trystan's Leigh's syndrome.

IX. Summary

After the Federal Circuit's mandate, the undersigned identified four issues within the scope of the Federal Circuit's remand. Order, issued June 12, 2020. While the reasoning is explained above, the resolution is set forth below concisely.

Issue A: Trystan's neurologic state in February 2009.

In February 2009, Trystan was neurologically normal.

Issue B: Trystan's health from end of February 2009 to end of May 2009.

During this time, Trystan suffered from colds periodically. He did not develop any neurologic problems until he began to lose skills no sooner than May 1, 2009. After May 1, 2009, he continued to lose skills.

Issue C: Trystan's health in August to October 2009.

From May to August and August to October 2009, Trystan declined neurologically. However, this decline does not constitute a rechallenge.

Issue D: Leigh's syndrome.

Trystan's compound heterozygous mutations are the sole substantial cause of his Leigh's syndrome.

X. Conclusion

The Sanchezes have demonstrated their love and concern for Trystan by, among other things, their persistence in this litigation. Through the Sanchezes' dedication, the Federal Circuit identified an error in the October 9, 2018 decision and remanded the case.

On remand, the corrected record does not show that the February 5, 2009 DTaP vaccination harmed Trystan. Although Trystan contorted his arm on February 16, 2009, this isolated event was not a manifestation of a neurologic problem. For the relevant time after the February 5, 2009 vaccine, Trystan was developing normally.

Furthermore, Trystan's genetic mutations are likely to be the sole substantial cause for his Leigh's syndrome. The genetic explanation constitutes an alternative reason to find that the vaccination did not harm Trystan.

Pursuant to Vaccine Rule 28.1(a), the Clerk's Office is instructed to deliver this decision to the judge assigned to this case. In the absence of a motion for review, the Clerk's Office is instructed to enter judgment in accord with this decision.

IT IS SO ORDERED.

s/ Christian J. Moran
Christian J. Moran
Special Master